

**IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
WICHITA FALLS DIVISION**

FRANCISCAN ALLIANCE, INC.,
et al.,

Plaintiffs,

v.

SYLVIA BURWELL, *et al.*,

Defendants.

No. 7:16-cv-00108

**Appendix to Plaintiffs' Brief
in Support of Their Motion
for Partial Summary
Judgment or,
in the Alternative,
Preliminary Injunction**

Respectfully submitted this the 21st day of October, 2016.

/s/ Luke W. Goodrich

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CERTIFICATE OF SERVICE

I hereby certify that on October 21, 2016 the appendix was served on Defendants via ECF.

/s/ Luke W. Goodrich

Luke W. Goodrich

Counsel for Plaintiffs Christian Medical & Dental Associations, Franciscan Health, Inc., Specialty Physicians of Illinois, LLC

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
WICHITA FALLS DIVISION

FRANCISCAN ALLIANCE, INC.;
SPECIALTY PHYSICIANS OF
ILLINOIS, LLC; CHRISTIAN
MEDICAL & DENTAL
ASSOCIATIONS;

– and –

STATE OF TEXAS;
STATE OF WISCONSIN;
STATE OF NEBRASKA;
COMMONWEALTH OF KENTUCKY,
by and through Governor Matthew G.
Bevin; STATE OF KANSAS; STATE OF
LOUISIANA; STATE OF ARIZONA; and
STATE OF MISSISSIPPI, by and
through Governor Phil Bryant.

Plaintiffs,

v.

SYLVIA BURWELL, Secretary of the
United States Department of Health and
Human Services; and UNITED STATES
DEPARTMENT OF HEALTH AND
HUMAN SERVICES,

Defendants

No. 7:16-cv-00108-O

**Declaration of Sister Jane Marie
Klein, OSF**

1. My name is Sister Jane Marie Klein. I am over the age of 21 and capable of making this declaration pursuant to 28 U.S.C. §1746. I have not been convicted of a felony or been convicted of a crime of dishonesty. I am Chairperson of the Board of Franciscan Alliance, Inc. I am also the liaison to our Provincial

Counsel of the Sisters of St. Francis of Perpetual Adoration for our healthcare ministry. I serve on all Divisional Boards of Franciscan Alliance. I had previously served as President of the Corporation and prior to that as President of two of the hospital facilities within the Corporation.

A. The Sisters of St. Francis and Franciscan Alliance

2. The Sisters of St. Francis of Perpetual Adoration were founded in 1863 by Mother Maria Theresia Bonzel in Olpe, Germany. From the beginning, the Sisters dedicated themselves to prayer—particularly the adoration of Jesus in the Blessed Sacrament—and to caring for those in need. The Sisters' first works were caring for orphans and providing home-based care to those who were too poor to afford treatment in a hospital. And the Sisters soon opened a school for higher learning for young women in Olpe as well. In 1875 the continuation of the Congregation was threatened by the severe restrictions under the Kulturkampf regime (of Otto von Bismark), which included an anticlerical reaction against the Catholic Church in Germany. The Congregation was forbidden to receive new candidates. The Convents were placed under police control and the Congregation's orphanage was closed. Mother Maria Theresia considered it wise to begin a new foundation for her Order in North America. In December 1875 she sent six of her Sisters to Lafayette, Indiana, to bring St. Francis of Assisi's ministry of healthcare and education to the Midwest United States. The first hospital building served as

both a convent and a hospital. Three weeks after their arrival, the Sisters admitted their first patient. They have continued their healthcare ministry ever since.

3. That ministry continues today through Franciscan Alliance Inc. ("Franciscan"), a Roman Catholic nonprofit hospital system founded by the Sisters. Franciscan is organized exclusively for charitable, religious, and scientific purposes within the meaning of Section 501(c)(3) of the Internal Revenue Code. Franciscan is incorporated in Indiana, with its principal place of business in Mishawaka, Indiana. The Sisters of St. Francis continue to serve as the sponsors of Franciscan.

4. The Members of Franciscan Alliance are all Sisters of the Congregation of the Sisters of St. Francis of Perpetual Adoration and they retain major reserve powers over the corporation. The Chair and the majority of the Board of Trustees are members of the Congregation. There are Sisters of the Congregation serving as Vice Presidents of Mission for each of the hospitals. Sisters also serve in other healthcare areas in the facilities including nursing and spiritual care.

5. Franciscan is now one of the strongest health systems in the country. Franciscan provides approximately 900 million dollars in Medicare and Medicaid services annually to the poor, disabled, and elderly. Franciscan also provides an additional approximately 500 million dollars per year in free and subsidized medical care, health clinics, and other benefits to the communities we serve, as reflected in

our annual community benefit reports.¹ Annually, Franciscan performs more than 4 million outpatient services and cares for more than 80,000 inpatients. Its major service locations have at least 2,900 beds and have a significant presence in their respective healthcare markets. Franciscan also receives annually approximately \$300,000 in HHS grants.

6. As part of its health care ministry, Franciscan operates Specialty Physicians of Illinois, LLC, another non-profit health care provider. Specialty Physicians is a nonprofit Illinois limited liability company with its principal place of business in Chicago Heights, Illinois. Specialty Physicians is a member managed limited liability company, of which Franciscan is the sole member. Specialty Physicians is organized exclusively for charitable, religious, and scientific purposes within the meaning of Section 501(c)(3) of the Internal Revenue Code. Specialty Physicians provides a myriad of physician specialist services in the South Suburban Chicago area. Specialty Physicians provides over 6 million dollars in Medicare and Medicaid services annually to the poor, disabled, and elderly. Annually, it performs approximately 90,000 outpatient services.

7. Since its founding over 140 years ago, Franciscan has remained fully committed to continuing the ministry of Jesus Christ through healthcare. All of Franciscan's hospitals provide resources to accommodate the spiritual needs of

¹ Franciscan Alliance, *Community Benefit Report* (2015), <http://sites.franciscanalliance.org/communitybenefit/2015/>.

employees, patients, and their families. These resources include Catholic priest chaplains, and chaplains of other faiths. Holy Communion, Reconciliation, Anointing of the Sick, Mass, Counseling, Hospice and Palliative Care support are among the spiritual care services provided.

8. Franciscan strives to provide top-quality care to its patients. Its facilities have earned designations as Centers of Excellence, Five-Star Awards, and top state and national rankings. In December of 2011, Franciscan was selected by the Center for Medicare & Medicaid Services ("CMS") as one of thirty-two Pioneer Accountable Care Organizations ("ACOs"). ACOs are groups of doctors, hospitals, and other healthcare providers who work together to give coordinated, high-quality care to their Medicare patients. The goal of the program is to ensure patients get timely and appropriate care while preventing medical errors and unnecessary duplicative services. The 2014 Quality Performance Report by CMS showed Franciscan placing in the top six for quality scores among all Pioneer ACOs.

9. One of Franciscan's specialties is in Women's and Children's healthcare services, a specialty which Franciscan advances in part by its Spirit of Women program. The program provides innovative clinical care, education, and wellness services.

10. Franciscan provides a wide variety of services specifically for women, such as obstetrics and gynecology services, hysterectomies, hormone treatments, and reconstructive surgery.

11. Franciscan is also affiliated with pediatric providers.

B. Franciscan's Values and Impact upon Care

12. Franciscan's infusion of faith into healthcare is not limited to spiritual support. All of Franciscan's healthcare services, and all of Franciscan's physicians and employees, follow the values of the Sisters of St. Francis in providing patient care. These values include:

- Respect for life: Treating each person with respect, dignity, fairness, and compassion so that each person is consciously aware of being loved.
- Fidelity to Franciscan's mission: Loyalty and pride in the healthcare facility are exemplified by members of the healthcare family through their joy and respect in empathetically ministering to patients, visitors and coworkers in the tradition of St. Francis of Assisi, bringing Christ's ministry of healing care to each patient, co-worker, and hospital visitor.
- Compassionate concern: Openness and concern for the welfare of the patients, especially the aged, the poor, and the disabled. The staff works with select associations and organizations to provide a continuum of care.
- Joyful service: The witness of Franciscan presence throughout the institution encompasses, but is not limited to, joyful availability, compassionate respectful care, and dynamic stewardship in the service of the church.
- Christian stewardship: Providing a just and fair allocation of human, spiritual, physical, and financial resources in a manner that respects the individual, is responsive to the needs of society, and follows the teaching of the Church.

13. In accordance with these values, Franciscan serves and respects individuals of all faith communities, seeking to ensure that patients and their

families can access the resources of their own faith traditions to assist in the healing and recovery process, and to make critical decisions about matters such as end-of-life care and clinical ethics.

14. In accordance with these values, all Franciscan facilities are operated in a manner that abides by *The Ethical and Religious Directives for Catholic Health Care Services*, as promulgated by the United States Conference of Catholic Bishops and interpreted by the local Bishop.

15. Consistent with these values and directives, Franciscan holds religious beliefs that sexual identity is an objective fact rooted in nature as male or female persons. Like the Catholic Church it serves, Franciscan believes that a person's sex is ascertained biologically, and not by one's beliefs, desires, or feelings. Franciscan believes that part of the image of God is an organic part of every man and woman, and that women and men reflect God's image in unique, and uniquely dignified, ways. Franciscan does not believe that government has either the power or the authority to redefine sex.

16. Accordingly, after careful review of this issue, Franciscan developed the following policy entitled the Sex Reassignment Interventions Policy: "Sexual reassignment interventions require a complex set of psychological, psychiatric and ancillary care services that are not available at Franciscan facilities. Therefore, it would be medically imprudent to perform or otherwise facilitate any clinical interventions addressing sexual re-assignment needs. To provide or otherwise

facilitate these services would also violate our deeply held religious beliefs.” A true and correct copy of that policy is attached as Ex. A. This policy is consistent with both Franciscan’s religious beliefs and its professional medical judgment.

17. Franciscan is committed to caring for patients with compassion and respect. Franciscan provides all of its standard medical services to every individual who needs and qualifies for its care, including to individuals who identify as transgender. Thus, for instance, if a transgender individual required cardiac care, Franciscan would provide the same full spectrum of compassionate care for that individual as it provides for every other cardiac patient. And, just as it does for every other cardiac patient, Franciscan would appropriately tailor that care to the biologically sex-specific health needs of the patient.

18. Franciscan believes that it would be dangerous to offer transition related-services without being able to offer a full continuum of care related to these services.

19. Also in keeping with its Catholic religious beliefs, Franciscan does not provide abortions or elective sterilizations.

20. Specialty Physicians shares Franciscan’s religious beliefs. As such, all of Specialty Physicians’ facilities are operated in a manner that abides by the same religious principles that apply to Franciscan.

21. Specialty Physicians has also adopted the same Sex Reassignment Intervention Policy as Franciscan. It also follows the same directives governing sterilization and abortion.

C. The Rule's Impact on Franciscan's Health Care Services

22. HHS's new Rule will impact Franciscan by 1) requiring Franciscan to offer medical services that violate its best medical judgment and religious beliefs, and 2) requiring Franciscan to provide insurance coverage for services that violate its religious beliefs.

23. Franciscan's hospitals, physicians and other employees provide a variety of health care services similar to those used in medical transitions. For example, Franciscan hospitals provide medically necessary hysterectomies and mastectomies to cancer patients and hormone treatments for patients facing endocrine disorders. But to provide these serious and life-altering services as part of a gender transition would require removing perfectly healthy organs and would violate both Franciscan's best medical judgment and its religious beliefs.

24. Franciscan employs physicians who offer endocrinology hormone services, hysterectomies, mastectomies, and psychiatric support. The new Rule would force Franciscan to offer these services as part of a medical transition, which would violate both Franciscan's best medical judgment and its religious beliefs.

25. Some of the procedures required under the Rule, including hysterectomies for gender transition, would also result in the sterilization of the

patient. Since Franciscan does not believe such a hysterectomy is medically necessary, being forced to provide such an elective sterilization procedure would violate Franciscan's best medical judgment and religious beliefs.

26. Franciscan's commitment to its religious beliefs requires it to forgo revenues that these services might generate. But Franciscan is willing, and committed, to forgo those revenues, because these services are contrary to Franciscan's religious beliefs and medical judgment.

27. In addition, Franciscan is committed to treating its patients with love, compassion, dignity, and respect. Franciscan does not believe that surgically removing healthy organs, or otherwise using surgical, chemical, or other means to try to change a person's biological sex, is consistent with Franciscan's commitment to treat that patient with love, compassion, dignity, and respect.

28. The Rule also prohibits discrimination on the basis of "termination of pregnancy." Franciscan performs surgical procedures for women who have miscarried a baby, such as dilation and curettage (D&C) procedures. However, Franciscan would be unwilling to offer the same service if the goal of the procedure was to terminate a pregnancy. The Rule pressures Franciscan to provide abortion-related procedures in violation of Franciscan's best medical judgment and religious beliefs.

29. While it does not perform abortions, Franciscan provides emergency services to women in compliance with EMTALA. Franciscan would provide

compassionate, high-quality care to a woman who, for example, needed emergency care for a complication that developed subsequent to an elective abortion.

30. The Rule will also impact Specialty Physicians. Specialty Physicians offers many services, such as endocrinology services, which will result in Specialty Physicians being impacted by the Regulation in the same manner as Franciscan, in that it will be forced to offer medical services that violate its religious beliefs under the new Regulation.

D. The Rule's Impact on Franciscan's Health Insurance Policies

31. As part of its religious practices, Franciscan also provides its employees with health benefits. Franciscan has over 17,000 employees, over 500 of which are physicians. Approximately 15,000 of these employees are eligible for health insurance benefits from Franciscan. Like its other operations, Franciscan's employee health benefits plan is operated in accordance with its religious beliefs. In accordance with those beliefs, Franciscan's plan specifically excludes coverage for any "[t]reatment, drugs, medicines, services, and supplies related to gender transition," as well as sterilizations and abortions.

32. Franciscan sincerely believes that providing insurance coverage for gender transition, sterilization, and abortion would harm its employees and constitute impermissible material cooperation with evil.

33. Franciscan sincerely believes that to terminate health insurance for its employees would be contrary to its religious commitment to a just and fair allocation of resources, in keeping with the teachings of the Catholic Church.

34. Franciscan has a health benefits plan that is administered by a third party administrator.

35. The Regulation also makes it more expensive for Franciscan to do business with its third party administrator. The Regulation subjects the third party administrator to potential liability for administering Franciscan's religious health plan, and thus Franciscan will be forced to indemnify its third party administrator from this liability.

36. Specialty Physicians shares the same beliefs, and offers the same type of insurance to its employees, as Franciscan.

37. Specialty Physicians has approximately 300 employees who are eligible for health insurance benefits. Specialty Physicians will face the same penalties as Franciscan for exercising its religious beliefs regarding its insurance policy under the Regulation.

E. The Rule's Burdens on Franciscan

38. Franciscan wants to be able to continue engaging in its religious exercise of providing high-quality compassionate care in accordance with its faith. Its ability to do so is chilled by this Rule, and by its lack of a clear safe harbor or exemption covering Franciscan.

39. Franciscan faces significant pressure to avoid speech regarding the experimental nature of transition related procedures, or speech that does not affirm a non-binary view of gender.

40. The Rule puts significant pressure on Franciscan medical professionals to express the view that gender transition procedures are not experimental. The Rule pressures Franciscan's medical professionals to express these views, even if they do not believe they are true, or even helpful for a patient.

41. The rule also pressures Franciscan to revise its written policies to conform to the government's view of the prudence of medical transition procedures and the need to offer those procedures, even though such a policy would run contrary to Plaintiffs' medical judgments, values, and religious beliefs.

42. The Rule also pressures Franciscan to provide insurance coverage for any transition-related procedure an employee's provider recommends to avoid significant liability.

43. Franciscan must now choose between (a) following its faith and its best medical judgment, or (b) following the Regulation. If it follows its faith and its medical judgment, Franciscan and its medical professionals will be subject to federal enforcement actions, loss of federal funding, potential debarment, lawsuits, and other potential penalties.

44. If Franciscan loses federal funding it will suffer a corresponding severe reduction in its capacity to carry out its religious mission to serve the poor, disabled,

and elderly. Franciscan already provides services to Medicaid patients at a loss, so any reduction in its Medicare or Medicaid funding will reduce its ability to provide services to the poor.

45. As part of its religious practices, Franciscan provides extensive medical services for the elderly, poor, and disabled. Many of those patients rely upon Medicare and Medicaid, and Franciscan provides approximately 900 million dollars in Medicare and Medicaid services annually to the poor, disabled, and elderly. Annually, it performs more than 4 million outpatient services and cares for more than 80,000 inpatients. Franciscan also receives annually approximately \$300,000 in HHS grants.

46. Specialty Physicians provides over 6 million dollars in Medicare and Medicaid services annually to the poor, disabled, and elderly. Annually, it performs approximately 90,000 outpatient services.

47. Those Medicare and Medicaid services are at risk if Franciscan continues to follow its religious beliefs and medical judgment regarding medical transitions, sterilizations, and abortions.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on October 18, 2016.



Sister Jane Marie Klein, OSF

EXHIBIT A

Current Status: Active

PolicyStat ID: 2661272



Franciscan

ALLIANCE

Original: 8/18/2016
 Last Reviewed: 8/18/2016
 Last Revised: 8/18/2016
 Next Review: 8/18/2019
 Responsible Party: Jane Marie Sister Klein:
 Chairwoman of the Board
 Policy Area: Administration
 References: Policy
 Applicability: Franciscan Alliance
 Corporate Board Directed -
 All

Sex Reassignment Interventions Policy

9/12/16 Franciscan Alliance hospital facility names were changed. See Hospital Listing document for new name changes and previous names.

Policy Number: 106.03

Applies to: All Franciscan Alliance Hospitals and all Franciscan Alliance Entities (See Entity Listing)

Policy:

Sexual reassignment interventions require a complex set of psychological, psychiatric and ancillary care services that are not available at Franciscan Alliance facilities. Therefore, it would be medically imprudent to perform or otherwise facilitate any clinical interventions addressing sexual re-assignment needs. To provide or otherwise facilitate these services would also violate our deeply held religious beliefs.

During the transition to PolicyStat, if you do not see any electronic signatures on this policy, the signatures will be found in the PDF archived version.

Attachments:

No Attachments

Approval Signatures

Committee	Approver	Date
Executive Committee of Franciscan Alliance, Inc.	Lethia Marie Sister Leveille: Corporate Secretary	8/18/2016
Legal Review by:	Pat Downes: Chief Legal Counsel [SC]	8/9/2016
Corporate Sponsor:	Jane Marie Sister Klein: Chairwoman of the Board [LL]	7/28/2016

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Plaintiffs,

v.

SYLVIA BURWELL, *et al.*,

Defendants.

No. 7:16-cv-00108-O

Declaration of Dr. David Stevens

1. My name is Dr. David Stevens. I am over the age of 21 and am capable of making this declaration pursuant to 28 U.S.C. §1746. I have not been convicted of a felony or crime involving dishonesty.

2. The facts contained herein are either within my personal knowledge, or contained in the records or documents of Christian Medical & Dental Associations (“CMDA”). If I were called upon to testify to these facts, I could and would competently do so.

3. I hold degrees from Asbury University, am an AOA graduate of the University of Louisville School of Medicine, and am trained in family practice. I earned a master’s degree in bioethics from Trinity International University in 2002. I also serve on the Board of Asbury University. I currently serve as a Fellow of the Biotechnology Policy Council of the Wilberforce Forum.

4. I am the Chief Executive Officer of the Christian Medical & Dental Associations, the nation’s largest faith-based organization of doctors.

5. Prior to my work with CMDA, I served as medical director of Samaritan's Purse. In Somalia, I led an emergency medical team that treated 45,000 suffering Somalis in the midst of war. In the Sudan, medical teams under my leadership treated over 25,000 villagers to stop the spread of an epidemic of relapsing fever causing a 40% mortality rate. My medical team was the first to enter Kigali, Rwanda and opened the largest hospital there while the genocide was still going on. From 1981 to 1991, I was a missionary doctor at Tenwek Hospital in Bomet, Kenya, where I served as Medical Superintendent and Executive Officer. I helped this facility grow from a "bush hospital" to a 300-bed tertiary care center which now does open- heart bypass surgery.

I. CMDA Purpose and Member Beliefs

6. CMDA is an Illinois non-profit corporation doing business as the Christian Medical & Dental Associations. Founded in 1931, and with a current membership of approximately 18,000, CMDA provides a variety of programs and services supporting its mission to "change hearts in healthcare."

7. CMDA membership is open to physicians and dentists or other healthcare professionals in the United States who are willing to sign CMDA's statement of faith. Over 60% of CMDA's membership is comprised of practicing physicians. The remainder consists of other categories of healthcare professionals, such as physician's assistants, nurses, dentists, or students studying to become physicians.

8. CMDA exists to glorify God by motivating, educating and equipping Christian healthcare professionals and students.

9. CMDA focuses on four result areas: 1) transformation, which involves helping Christian healthcare professionals integrate their faith into their practice, 2) service, which includes mission outreach and education both international and domestic and providing services to vulnerable populations, 3) equipping, which includes enabling members to have the tools they need to be effective in their practice, and 4) voice, which includes representing members at both the federal and state levels on important issues impacting members.

10. One of CMDA's key priorities is to act as a voice of its members in the public square. In doing so, CMDA does for its members what they are often unable to do alone because of restrictions in healthcare practice. CMDA is able to unite the voices of its members on important issues.

11. On behalf of its members, CMDA promotes positions and addresses policies on healthcare issues; serves others through overseas medical mission projects; coordinates a network of Christian healthcare professionals for fellowship and professional growth; sponsors student ministries in medical and dental schools; distributes educational resources; provides continuing education for doctors serving missions in developing countries; and conducts academic exchange programs overseas.

12. CMDA members sign a statement of faith to join CMDA and allow CMDA to serve as a voice for membership values. *See* CMDA, *Our Mission & Vision*, <https://cmda.org/about/page/our-mission-vision> (last visited Oct. 21, 2016).

13. One of CMDA's other key priorities is the adoption of ethical guidelines reflecting the beliefs of its members.

14. To that end, CMDA's National Convention has adopted a Transgender Identification Ethics Statement on transgender identity that was approved by its House of Delegates unanimously. This Ethics Statement explains the medical, ethical, and religious beliefs of CMDA members, specifically with regard to facilitating or encouraging gender transition. A true and correct copy of the Transgender Identification Ethics Statement is attached as Exhibit A.

15. The Transgender Identification Ethics Statement was developed with input from medical professionals with expertise in general pediatrics, psychiatry, internal medicine, general surgery, plastic surgery, hematology, pathology, and critical care, among others. This Statement outlines a number of health risks associated with gender transition medical procedures. It notes, for example, that cross-hormone therapy can increase the risk of negative health outcomes, and can also inhibit normal growth and fertility. *See* Ex. A at 2. Indeed, endocrine guidance on the treatment of transgender individuals acknowledges that endocrine treatment can have "potentially irreversible effects" on the fertility of transgender individuals, associated in part with "testicular damage" in males and "increased incidence of

polycystic ovaries” in females. *See* Ex. B, Endocrine Treatment of Transsexual Persons. And one study found that puberty blocking medication used during adolescence can result in decreased height and loss of bone mineral density. *See* Ex. C at 194, Pasquino, Pucarelli, Accardo, Demiraj, Segni, & Nardo. The CMDA Statement also observes that surgical alteration gender transition procedures have uncertain and sometimes harmful effects for patients. *See* Ex. A at 2.

16. The CMDA Statement discusses the fact that gender questioning can often occur during childhood, and evidence suggests that “gender identity has some degree of malleability, and is influenced by psychosocial experiences.” *See* Ex. A at 2. In fact, follow-up studies with individuals who experienced gender dysphoria as youth found that this gender dysphoria most often desisted as adults. *See* Ex. D, Singh at 104 (“Of the 139 participants, . . . 122 (87.8%) were classified as desisters at follow-up.”); Ex. E, Drummond, K. D., Bradley, S. J., Peterson-Badali, M., & Zucker, K. J. at 39 (“22 participants (88%) reported no distress with their female gender identity at follow-up. None of the participants desired contrasex hormones or sex reassignment surgery to masculinize their bodies, nor did they express a desire to get rid of their female sex characteristics.”); Ex. F, Wallien, M. S. C., & Cohen-Kettenis at 1413 (“Most children with gender dysphoria will not remain gender dysphoric after puberty.”); *see also* Ex. G at 746, Zucker KJ, Gender Identity Disorder (noting that one follow-up study showed that only 1 out of 44 gender dysphoric males were still gender dysphoric in adulthood to the extent of

considering sex-reassignment surgery). As a result of the numerous medical and physiological risks associated with gender transition procedures, CMDA's Statement thus noted that "attempts to alter gender surgically or hormonally . . . are medically inappropriate." *See* Ex. A at 1.

17. CMDA members also have religious objections to participating in or providing insurance coverage for abortions. CMDA has an Ethics Statement on abortion, which states in part, "We oppose the practice of abortion and urge the active development and employment of alternatives." CMDA also has an Ethics Statement on moral complicity, stating that just as its members "strive to never commit" certain conduct themselves, they also should not "participate in or encourage" such conduct with "others." The document also states that moral complicity "may involve enabling or facilitating future immoral actions of patients or professionals." A true and correct copy of the Ethics Statement on moral complicity is attached as Exhibit H. Thus, CMDA members have religious objections to providing insurance coverage for objectionable services. That is why CMDA has publicly advocated for protections for CMDA members regarding abortion insurance coverage alongside other coalition groups. *See* Ex. I, Joint Coalition Letter re Conscience Protection Act (April 2016).

II. Impact of HHS Rule on CMDA Members

18. Many CMDA members provide medical services in other contexts that may be requested as part of a gender transition. For example, some CMDA

members provide hysterectomies to treat conditions such as cancer, and, given the nature of their practice, may be asked to remove a healthy uterus as part of a gender transition. Some CMDA members provide puberty-blocking medication to children with a medical disorder known as precocious puberty, and, given the nature of their practice, may be asked to provide puberty-blocking medication to a child whose mental health provider diagnoses gender dysphoria. Some CMDA members provide hormone medication to patients, including children, for medical reasons related to insufficient hormone production, and, given the nature of their practice, may be asked to offer cross-hormone therapy to patients, including children, who have been referred for gender dysphoria. Some CMDA members perform mastectomies for women who have breast cancer, and, given the nature of their practice, may be asked to perform mastectomies for a woman for a gender transition purpose. Some CMDA members perform breast reconstruction for women who have undergone mastectomies, and, given the nature of their practice, may be asked to construct breasts for men undergoing a gender transition. Some CMDA members counsel patients to help them accomplish mental health goals, and, given the nature of their practice, may be asked to facilitate gender transition as a viable mental health alternative based on a non-binary view of gender.

19. In accordance with CMDA's Transgender Identification Ethics statement, these members would counsel (and in some cases have counseled) patients against pursuing gender transition and have privately or publicly

discussed the risks and concerns related to gender transition procedures. In light of the new Rule, these members are very concerned that they will face liability if they continue to do so. They now face significant pressure to affirm the provision of gender transition procedures in medical policies, and to affirm a non-binary view of gender.

20. Many CMDA members also provide health coverage for employees and believe, in accordance with CMDA's Transgender Identification Ethics Statement, that they cannot collaborate with "interventions to alter normal sexual anatomy to conform to transgender desires." *See* Ex. A at 2. Nor can they collaborate with abortion. To provide health insurance to cover these procedures would be to collaborate with medical procedures which are contrary to the members' religious beliefs and would therefore violate their faith. *See* Ex. H.

21. Many CMDA members accept Medicare and Medicaid patients, and others accept other forms of federal funding, making them subject to the Rule.

22. In light of HHS's new Rule, CMDA members are very concerned about the loss of large Medicare and Medicaid payments along with other federal grants and funding, federal enforcement actions, private lawsuits, and inability to serve the poor, elderly, and disabled—all for following their medical judgment and religious beliefs and declining to perform medical transition procedures.

23. In light of the new Rule, I am aware of many CMDA members who are concerned about liability that could result from publicly and candidly expressing

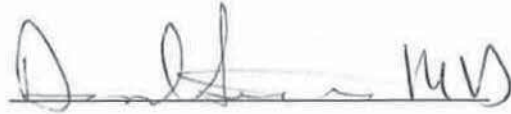
their medical, ethical, or religious views about concerns related to gender transition procedures. I am also aware of many CMDA members who are concerned that they will face liability for honestly advising patients about the risks and experimental nature of gender transition procedures.

24. CMDA members have treated and do treat individuals who identify as transgender, for health issues ranging from common colds to cancer. As stated in CMDA's ethics statement, they serve these patients with sensitivity and compassion. A number of these members have begun receiving requests from patients for gender-transition related procedures. Because our members believe that encouraging or participating in a gender transition would be inappropriate for medical, ethical, and religious reasons, they cannot comply with these requests.

25. In a rigorous survey of 2,865 faith-based healthcare professionals conducted by The Polling Company, Inc., in April 2009, the results showed that 91% of physicians agreed, "I would rather stop practicing medicine altogether than be forced to violate my conscience." A true and correct copy of the survey results is attached as Exhibit J. I am personally aware of CMDA members who have recently decided to leave the medical field because they faced significant pressure to violate their conscience. Many of these members were in the prime of their career, and their departure is a significant loss to the field of medicine.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on October 21, 2016.

A handwritten signature in dark ink, appearing to read "D. Stevens", written over a horizontal line.

DR. DAVID STEVENS

EXHIBIT A



Transgender Identification

CMDA affirms the historic and enduring Christian understanding of humankind as having been created male and female. CMDA has concerns about recent usage of the term “gender” to emphasize an identity other than one’s biological sex, that is, a sense of self based on subjective feelings or desires of identifying more strongly with the opposite sex or with some combination of male and female.^{1,2,3,4,5}

CMDA affirms the obligation of Christian healthcare professionals to care for patients struggling with gender identity with sensitivity and compassion. CMDA holds that attempts to alter gender surgically or hormonally for psychological indications, however, are medically inappropriate, as they repudiate nature, are unsupported by the witness of Scripture, and are inconsistent with Christian thinking on gender in every prior age. Accordingly, CMDA opposes medical assistance with gender transition on the following grounds.

A. Biblical

1. God created humanity as male and female (Genesis 1:27, 5:2; Matthew 19:4; Mark 10:6). God’s directives – to have dominion over the earth and to fulfill his goals of procreation, union, fellowship, and worship – are given to men and women together (Genesis 1:26-28, 2:18-24).
2. Men and women are morally and spiritually equal (Galatians 3:28) and are created to have roles that are in some respects alike and in other respects wonderfully complementary (Ephesians 5). (See CMDA statement on Human Sexuality)
3. All people are loved by God (John 3:16-17). All struggle with moral failure and fall short of God’s standards (Romans 3:10-12) and, therefore, need the forgiveness that God provides through Christ alone (John 3:36; Romans 3:22-24; Colossians 1:15-22; 1 Timothy 2:5-6).
4. We live in a fallen world (Genesis 3), and we are all fallen creatures with a sinful nature (Romans 3:9-12). The fall is expressed in nature and in humanity in many ways, including sexuality. Confusion of gender identity is but one example of the fall, as are also marital breakdown and sexual immorality (Romans 1:24-32; Ephesians 5:3).
5. A lifestyle that is directed by pursuing sexual desires or governed by personal sexual fulfillment^{6,7,8} misses the divinely ordained purpose of sex, which is for procreation and for facilitating unity in the lifelong commitment of marriage between one man and one woman, which fosters a secure and nurturing environment for children and which reflects the unity of Christ and the church (Exodus 20:1-18; Leviticus 20:10-21; Romans 1; Ephesians 5:23-33).

B. Biological

1. Sex is an objective biological fact that is determined genetically at conception by the allocation of X and Y chromosomes to one’s genome, immutable throughout one’s lifetime, and not a social construct arbitrarily assigned at birth or changed at will.
2. Human beings are sexually dimorphic. Male and female phenotypes are the outworking of sex gene expression, which shapes sex anatomy, determines patterns of sex hormone secretion, and influences sex differences in the development of the central nervous system and other organs.
3. Procreation requires genetic contributions from both one man and one woman.
4. Anomalies of human biological sex are an outcome of the fall and do not invalidate God’s design in creation.

C. Social

1. CMDA recognizes that gender identity issues are complex, and inclination to identify with the opposite gender may have biological, familial, and social origins that are not of the making of particular individuals.⁹
2. In our current social context there is a prevailing view that removing traditional definitions and boundaries is a requirement for self-actualization. Thus, Christian healthcare professionals find themselves in the position of being at variance with evolving views of gender identity in which patients seek validation by the

medical community of transsexual desires and choices that may be socially approved but which are contrary to a Christian worldview.

3. In contrast to the current culture, CMDA believes that finding one's identity within God's design will result in a more healthy and fulfilled life. CMDA believes, moreover, that social movements which contend that gender is decided by choice are mistaken in defining gender, not by nature, but according to desire. Authentic personal identity consists in social gender expression that is congruent with one's natural biological sex. CMDA recognizes that this traditional view has become counter-cultural; however, CMDA affirms that God's design transcends culture.
4. CMDA is concerned that efforts to impose transgender ideology on all society by excluding, suppressing, marginalizing, intimidating, or portraying as hateful those individuals and organizations which, on scientific, moral, or religious grounds, reasonably disagree, are contrary to the freedoms of speech and religious liberty that lie at the very foundation of a just and democratic society.^{10,11}
5. CMDA is concerned that efforts to compel healthcare professionals to affirm transgender ideology, provide medical legitimization for transgender psychology, or cooperate with requests for medical or surgical sex reassignment threaten professional integrity.

D. Medical

1. Among individuals who identify as transgender, use cross-sex hormones, and undergo sex reassignment surgery, there is well-documented increased incidence of depression, anxiety, suicidal ideation, substance abuse, and risky sexual behaviors.^{12,13,14,15,16,17,18,19,20,21} Patients' gender-altering and sexual encounter choices are among the factors relevant to these health disparities in transgender patients as compared to the general population.^{22,23,24}
2. Hormones prescribed to a previously biologically healthy child for the purpose of blocking puberty inhibit normal growth and fertility.²⁵ Continuation of cross-sex hormones, such as estrogen and testosterone, during adolescence is associated with increased health risks including, but not limited to, high blood pressure, blood clots, stroke, and some types of cancer.^{26,27,28,29}
3. Although current medical evidence is incomplete and open to various interpretations, some studies suggest that surgical alteration of sex characteristics has uncertain and potentially harmful psychological effects and can mask or exacerbate deeper psychological problems.^{30,31,32}
4. Transient gender questioning can occur during childhood. There is evidence that gender identity has some degree of malleability and is influenced by psychosocial experiences, including therapeutic interventions.^{33,34,35,36,37,38}
5. CMDA recognizes that exceedingly rare abnormalities exist in which chromosomal and phenotypic sex characteristics are in discord. These disorders of sex development include congenital adrenal hyperplasia, ambiguous genitalia, and androgen insensitivity syndrome. Treatment of these disorders differs categorically from transgender interventions, which are performed on persons whose sex phenotype is in agreement with their chromosomal sex designation.

E. Ethical

1. Medicine rests on science and should not be held captive to desires or demands that contradict biological reality. Sex reassignment operations are physically harmful because they disregard normal human anatomy and function. Normal anatomy is not a disease; dissatisfaction with natural anatomical and genetic sexual makeup is not a condition that can be successfully remedied medically or surgically.
2. The medical status of gender identity disorder as a mental or psychosocial disorder should not be discarded on the basis of social activism.
3. For Christians struggling with transgender inclinations, spiritual, psychological, and social support are needed, as attempts to change gender through hormonal or surgical interventions only lead to further spiritual turmoil and distress.
4. CMDA is especially concerned about the increasing phenomenon of parents of children who question their gender intervening hormonally to inhibit normal adolescent development.^{25,39,40,41,42,43} Children lack the developmental cognitive capacity to assent or request such interventions, which have lifelong physical, psychological, and social consequences.⁴⁴
5. The purpose of medicine is to heal the sick, not to collaborate with psychosocial disorders. Whereas treatment of anatomically anomalous sexual phenotypes is restorative, interventions to alter normal sexual anatomy to conform to transgender desires are disruptive to health.⁴⁵
6. The inability of men, including men who identify as women, to bear children is not an illness to be remedied by medical or surgical means, such as uterus transplantation.
7. Many diseases affect men and women differently, according to biological sex phenotype. Transgender designations may conceal biological sex differences relevant to medical risk factors, recognition of which is

important for effective healthcare and disease prevention. As accurate documentation is necessary for good patient care, healthcare professionals should document patients' biological sex and any alterations of gender characteristics factually in the medical record.

CMDA Recommendations for the Christian Community

1. A person struggling with gender identity should evoke neither scorn nor enmity, but rather our concern, compassion, help, and understanding. Christians must respond to the complex issues surrounding gender identity with grace, civility, and love.
2. The Christian community must help society understand that gender complementarity and fixity are both good and a part of the natural order. CMDA is concerned that attempting to reconstruct gender as something that is fluid and changeable through technical means would have grave spiritual, emotional, cultural, and medical repercussions.
3. The Christian community and especially the family must resist stereotyping or rejecting individuals who do not fit the popular norms of masculinity and femininity. Parents should guide their children in appropriate gender identity development. For children who are experiencing gender identity confusion, the Christian community should provide appropriate role models and informed guidance.
4. The Christian community must condemn hatred and violence directed against those struggling with gender identity. Love for the person does not equate with support of the decision to change sex anatomy or gender identity.
5. For the sake of the common good, Christians should welcome inclusion of transgender individuals but oppose claims to grant special rights based solely on transgender identification.
6. The Christian community is to be a refuge of love for all who are broken – including sexually broken – not to affirm their sin, nor to condemn or castigate, but to shepherd them to Jesus, who alone can forgive, heal, restore, and redirect to a Godly, honorable, and virtuous way of life. God provides the remedy for all moral failure through faith in Jesus Christ and the life-changing power of the Holy Spirit.

CMDA Recommendations for Christian Healthcare Professionals

1. CMDA advocates culturally competent medical care of patients who identify as transgender. Such care requires our compassion, an open and trusting dialogue, a genuine effort to understand and respond to the patient's psychological distress, and acceptance of the person without necessarily agreeing with the person's ideology or providing a requested sex-altering intervention.
2. CMDA believes that the appropriate medical response to patients with gender confusion should be to support and encourage them in areas we can affirm and to help them understand themselves as people God loves and who are made in his image, even when we cannot validate their choices. We should validate their right as individuals in a free society to make decisions for themselves, while explaining that their right does not extend to obligating the healthcare professional to prescribe medication or perform surgical procedures that we believe to be harmful, such as interventions that deface, disfigure, or mutilate the patient's biological sex.
3. CMDA believes that Christian physicians should not engage in hormonal and surgical interventions that alter natural sex phenotypes, as this contradicts the basic principles of Christian medical ethics, which regards medical treatment as intended to heal and not to harm.
4. CMDA believes that prescribing hormonal treatments to children or adolescents to disrupt normal sexual development for the purpose of gender reassignment is ethically impermissible, whether requested by the child or the parent. (See CMDA statements on Limits to Parental Authority in Medical Decision-Making, and Abuse of Human Life)

CMDA Recommendations Regarding Nondiscrimination

1. Mutual respect and civil discourse are cornerstones of a free society. The Christian healthcare professional should respect how a patient wishes to be addressed.
2. Christian healthcare professionals, in particular, must care for their patients with gender identity disorders in a non-judgmental and compassionate manner, consistent with the humility Jesus modeled and the love Jesus commanded us to show all people.
3. Those who hold to a biblical or traditional view of human sexuality should be permitted to question transgender dogma free from exclusion, oppression, or unjust discrimination. Healthcare professionals who hold the position that transgender identification is harmful and inconsistent with the will of God should not be stigmatized or accused of being bigoted, phobic, unprofessional, or discriminatory because of this sincerely held and widely shared belief.
4. To decline to provide a requested gender-altering treatment that is harmful or is not medically indicated does not constitute unjust discrimination against persons. CMDA affirms that healthcare professionals

should not be coerced or mandated to provide or refer for services that they believe to be morally wrong or harmful to patients. (See CMDA statement on Healthcare Right of Conscience)

5. Healthcare professionals must not be prevented from providing counseling and support to patients who are experiencing confusion in regard to gender orientation and who request assistance with accepting and maintaining their biologic sex and gender identity.

*Unanimously approved by the House of Representatives
April 21, 2016
Ridgcrest, North Carolina*

¹ Stoller RJ. A contribution to the study of Gender Identity. *Int J Psychoanal* 1964; 45: 220-226.

² Buchholz L. Transgender care moves into the mainstream. *JAMA* 2015; 314(17): 1785-1787.

³ Drescher J. Queer diagnoses revisited: The past and future of homosexuality and gender diagnoses in DSM and ICD. *Int Rev Psychiatry* 2015; 27(5): 386-395.

⁴ Diamond M. Sex, gender, and identity over the years: a changing perspective. *Child Adolesc Psychiatric Clin N Am* 2004; 13(3): 591-607.

⁵ Green R, Money J. Incongruous gender role: nongenital manifestations in prepubertal boys. *J Nerv Ment Dis* 1960; 131: 160-168.

⁶ Lawrence AA. Autogynephilia: an underappreciated paraphilia. *Adv Psychosom Med* 2011; 31: 135-148.

⁷ Hsu KJ, Rosenthal AM, Miller DI, Bailey JM. Who are gynandromorphophilic men? Characterizing men with sexual interest in transgender women. *Psychol Med* 2015 Oct 26: 1-9.

⁸ Blanchard R. Varieties of autogynephilia and their relationship to gender dysphoria. *Arch Sex Behav* 1993; 22(3): 241-251.

⁹ Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrinol Metabol* 2014; 99(12): 4379-4389.

¹⁰ First Amendment to the United States Constitution; Article 18 of the United Nations Universal Declaration of Human Rights.

¹¹ Morabito S. The transgender war against human rights, science, and consent. *The Federalist*, February 23, 2016. Accessed at: <http://thefederalist.com/2016/02/23/the-transgender-war-against-human-rights-science-and-consent/>

¹² Bariola E, Lyons A, Leonard W, et al. Demographic and psychosocial factors associated with psychological distress and resilience among transgender individuals. *Am J Public Health* 2015; 105(10): 2108-2116.

¹³ Bauer GR, Scheim AI, Pyne J, et al. Intervenable factors associated with suicide risk in transgender persons: a respondent driven sampling study in Ontario, Canada. *BMC Public Health* 2015; 15: 525. DOI 10.1186/s12889-015-1867-2

¹⁴ Budge SL, Adelson JL, Howard KA. Anxiety and depression in transgender individuals: the roles of transition status, loss, social support, and coping. *J Consult Clin Psychol* 2013; 81(3): 545-557.

¹⁵ Dhejne C, Lichtenstein P, Boman M, et al. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011 Feb 22; 6(2): e16885. doi: 10.1371/journal.pone.0016885.

¹⁶ Krehely J. How to close the LGBT Health Disparities Gap. Center for American Progress, December 21, 2009. "LGBT people are at a higher risk for cancer, mental illnesses, and other diseases, and are more likely to smoke, drink alcohol, use drugs, and engage in other risky behaviors." Accessed at: https://www.americanprogress.org/wp-content/uploads/issues/2009/12/pdf/lgbt_health_disparities.pdf

¹⁷ Levine SB, Solomon A. Meanings and political implications of "psychopathology" in a gender identity clinic: a report of 10 cases. *J Sex Marital Ther* 2009; 35(1): 40-57.

¹⁸ Rajkumar RP. Gender identity disorder and schizophrenia: neurodevelopmental disorders with common causal mechanisms? *Schizophr Res Treatment* 2014; 2014:463757. doi: 10.1155/2014/463757.

¹⁹ Reisner SL, Vettters R, Leclerc M, et al. Mental health of transgender youth in care at an adolescent urban community health center: A matched retrospective cohort study. *J Adolesc Health* 2015; 56(3): 274-279.

²⁰ Rowe C, Santos GM, McFarland W, Wilson EC. Prevalence and correlates of substance use among trans female youth ages 16-24 years in the San Francisco Bay Area. *Drug Alcohol Depend* 2015; 147: 160-166.

- ²¹ Haas AP, Rodgers PL, Herman JL. Suicide attempts among transgender and gender non-conforming adults. The Williams Institute, January 2014. Accessed at: <http://williamsinstitute.law.ucla.edu/wp-content/uploads/AFSP-Williams-Suicide-Report-Final.pdf>
- ²² Centers for Disease Control and Prevention, About LGBT Health, March 25, 2014. "Differences in sexual behavior account for some of these disparities." Accessed at: <http://www.cdc.gov/lgbthealth/about.htm>
- ²³ Clements-Nolle K, Marx R, Guzman R, Katz M. HIV Prevalence, Risk Behaviors, Health Care Use, and Mental Health Status of Transgender Persons: Implications for Public Health Intervention. *J Public Health* 2001; 91: 915-921. "Many engage in behaviors that put them at risk for HIV."
- ²⁴ Bauer GR, Travers R, Scanlon K, Coleman TA. High heterogeneity of HIV-related sexual risk among transgender people in Ontario, Canada: a province-wide respondent-driven sampling survey. *BMC Public Health* 2012; 12: 292. "Several small- to moderate-size studies report high proportions of FTMs engaging in high-risk sex." Accessed at: <http://www.biomedcentral.com/1471-2458/12/292>
- ²⁵ Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal A, et al. Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009; 94(9): 3132-3154.
- ²⁶ Olson-Kennedy J, Forcier M. Overview of the management of gender nonconformity in children and adolescents. UpToDate November 4, 2015. Accessed March 20, 2016 at www.uptodate.com.
- ²⁷ Moore E, Wisniewski A, Dobs A. Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. *J Clin Endocrinol Metab* 2003; 88(8): 3467-3473.
- ²⁸ FDA Drug Safety Communication issued for testosterone products. [Http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161874.htm](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161874.htm).
- ²⁹ World Health Organization Classification of Estrogen as a Class I Carcinogen. [Http://www.who.int/reproductivehealth/topics/ageing/cocs_hrt_statement.pdf](http://www.who.int/reproductivehealth/topics/ageing/cocs_hrt_statement.pdf).
- ³⁰ McHugh PR. Transgender surgery isn't the solution. *The Wall Street Journal*, June 12, 2014. Accessed at: <http://www.wsj.com/articles/paul-mchugh-transgender-surgery-isnt-the-solution-1402615120>
- ³¹ McHugh PR. Surgical sex: why we stopped doing sex change operations. *First Things* November 2004, pp. 34-38. Accessed at: <http://www.firstthings.com/article/2004/11/surgical-sex>
- ³² Köhler B, Kleinemeier E, Lux A, et al. Satisfaction with genital surgery and sexual life of adults with XY disorders of sex development: results from the German clinical evaluation study. *J Clin Endocrinol Metab* 2012; 97(2): 577-588.
- ³³ Zucker KJ. Gender identity development and issues. *Child Adolesc Psychiatr Clin N Am* 2004; 13(3): 551-568. "...because GID seems to desist in most children, it seems that gender identity has some degree of malleability that likely is influenced by psychosocial experiences, including therapeutic interventions."
- ³⁴ Zucker KJ, Wood H, Singh D, Bradley SJ. A developmental, biopsychosocial model for the treatment of children with gender identity disorder. *J Homosex* 2012; 59(3): 369-397.
- ³⁵ Bradley SJ, Steiner B, Zucker K, et al. Gender identity problems of children and adolescents: the establishment of a special clinic. *Can Psychiatr Assoc J* 1978; 23(3): 175-183.
- ³⁶ Zucker KJ. On the "natural history" of gender identity disorder in children. *J Am Acad Child Adolesc Psychiatry* 2008; 47(12): 1361-1363.
- ³⁷ Zucker KJ, Bradley SJ, Doering RW, Lozinski JA. Sex-typed behavior in cross-gender-identified children: stability and change at a one-year follow-up. *J Am Acad Child Psychiatry* 1985; 24(6): 710-719.
- ³⁸ Zucker KJ, Bradley SJ, Kuksis M, et al. Gender constancy judgments in children with gender identity disorder: evidence for a developmental lag. *Arch Sex Behav* 1999; 28(6): 475-502.
- ³⁹ Adelson SL, American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter on gay, lesbian, or bisexual orientation, gender nonconformity, and gender discordance in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 2012; 51(9): 957-974.
- ⁴⁰ Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. *J Pediatr* 2014; 164(4): 906-911.
- ⁴¹ Vrouenraets LJJJ, Fredriks AM, Hannema SE, et al. Early medical treatment of children and adolescents with gender dysphoria: an empirical ethical study. *J Adolesc Health* 2015; 57(4): 367-373.
- ⁴² Wiesemann C, Ude-Koeller S, Sinnecker GHG, Thyen U. Ethical principles and recommendations for the medical management of differences of sex development (DSD)/intersex in children and adolescents. *Eur J Pediatr* 2010; 169: 671-679.

⁴³ Smith WJ. Sex change treatment for 7 year olds! *First Things* blog, May 19, 2008. Accessed at: <http://www.firstthings.com/blogs/firstthoughts/2008/05/sex-change-treatment-for-7-year-olds>

⁴⁴ Diamong M, Garland J. Evidence regarding cosmetic and medically unnecessary surgery on infants. *J Pediatr Urol* 2014; 10(1): 2-6.

⁴⁵ Daly TTW. Gender dysphoria and the ethics of transsexual (i.e., gender reassignment) surgery. *Ethics & Medicine* 2016; 32(1): 39-53.

EXHIBIT B

Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline

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Objective: The aim was to formulate practice guidelines for endocrine treatment of transsexual persons.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low.

Consensus Process: Committees and members of The Endocrine Society, European Society of Endocrinology, European Society for Paediatric Endocrinology, Lawson Wilkins Pediatric Endocrine Society, and World Professional Association for Transgender Health commented on preliminary drafts of these guidelines.

Conclusions: Transsexual persons seeking to develop the physical characteristics of the desired gender require a safe, effective hormone regimen that will 1) suppress endogenous hormone secretion determined by the person's genetic/biologic sex and 2) maintain sex hormone levels within the normal range for the person's desired gender. A mental health professional (MHP) must recommend endocrine treatment and participate in ongoing care throughout the endocrine transition and decision for surgical sex reassignment. The endocrinologist must confirm the diagnostic criteria the MHP used to make these recommendations. Because a diagnosis of transsexualism in a prepubertal child cannot be made with certainty, we do not recommend endocrine treatment of prepubertal children. We recommend treating transsexual adolescents (Tanner stage 2) by suppressing puberty with GnRH analogues until age 16 years old, after which cross-sex hormones may be given. We suggest suppressing endogenous sex hormones, maintaining physiologic levels of gender-appropriate sex hormones and monitoring for known risks in adult transsexual persons. (*J Clin Endocrinol Metab* 94: 3132–3154, 2009)

Summary of Recommendations

1.0 Diagnostic procedure

1.1 We recommend that the diagnosis of gender identity disorder (GID) be made by a mental health profes-

sional (MHP). For children and adolescents, the MHP should also have training in child and adolescent developmental psychopathology. (1 ⊕⊕○○)

1.2 Given the high rate of remission of GID after the onset of puberty, we recommend against a complete social

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Abbreviations: BMD, Bone mineral density; FTM, female-to-male; GID, gender identity disorder; MHP, mental health professional; MTF, male-to-female; RLE, real-life experience.

role change and hormone treatment in prepubertal children with GID. (1 ⊕⊕○○)

1.3 We recommend that physicians evaluate and ensure that applicants understand the reversible and irreversible effects of hormone suppression (*e.g.* GnRH analog treatment) and cross-sex hormone treatment before they start hormone treatment.

1.4 We recommend that all transsexual individuals be informed and counseled regarding options for fertility prior to initiation of puberty suppression in adolescents and prior to treatment with sex hormones of the desired sex in both adolescents and adults.

2.0 Treatment of adolescents

2.1. We recommend that adolescents who fulfill eligibility and readiness criteria for gender reassignment initially undergo treatment to suppress pubertal development. (1 ⊕○○○)

2.2. We recommend that suppression of pubertal hormones start when girls and boys first exhibit physical changes of puberty (confirmed by pubertal levels of estradiol and testosterone, respectively), but no earlier than Tanner stages 2–3. (1 ⊕⊕○○)

2.3. We recommend that GnRH analogs be used to achieve suppression of pubertal hormones. (1 ⊕⊕○○)

2.4. We suggest that pubertal development of the desired opposite sex be initiated at about the age of 16 yr, using a gradually increasing dose schedule of cross-sex steroids. (2 ⊕○○○)

2.5. We recommend referring hormone-treated adolescents for surgery when 1) the real-life experience (RLE) has resulted in a satisfactory social role change; 2) the individual is satisfied about the hormonal effects; and 3) the individual desires definitive surgical changes. (1 ⊕○○○)

2.6 We suggest deferring surgery until the individual is at least 18 yr old. (2 ⊕○○○)

3.0 Hormonal therapy for transsexual adults

3.1 We recommend that treating endocrinologists confirm the diagnostic criteria of GID or transsexualism and the eligibility and readiness criteria for the endocrine phase of gender transition. (1 ⊕⊕⊕○)

3.2 We recommend that medical conditions that can be exacerbated by hormone depletion and cross-sex hormone treatment be evaluated and addressed prior to initiation of treatment (see Table 11: Medical conditions that can be exacerbated by cross-sex hormone therapy). (1 ⊕⊕⊕○)

3.3 We suggest that cross-sex hormone levels be maintained in the normal physiological range for the desired gender. (2 ⊕⊕○○)

3.4 We suggest that endocrinologists review the onset and time course of physical changes induced by cross-sex hormone treatment. (2 ⊕⊕○○)

4.0 Adverse outcome prevention and long-term care

4.1 We suggest regular clinical and laboratory monitoring every 3 months during the first year and then once or twice yearly. (2 ⊕⊕○○)

4.2 We suggest monitoring prolactin levels in male-to-female (MTF) transsexual persons treated with estrogens. (2 ⊕⊕○○)

4.3 We suggest that transsexual persons treated with hormones be evaluated for cardiovascular risk factors. (2 ⊕⊕○○)

4.4 We suggest that bone mineral density (BMD) measurements be obtained if risk factors for osteoporosis exist, specifically in those who stop hormone therapy after gonadectomy. (2 ⊕⊕⊕○)

4.5 We suggest that MTF transsexual persons who have no known increased risk of breast cancer follow breast screening guidelines recommended for biological women. (2 ⊕⊕○○)

4.6 We suggest that MTF transsexual persons treated with estrogens follow screening guidelines for prostatic disease and prostate cancer recommended for biological men. (2 ⊕○○○)

4.7 We suggest that female-to-male (FTM) transsexual persons evaluate the risks and benefits of including total hysterectomy and oophorectomy as part of sex reassignment surgery. (2 ⊕○○○)

5.0 Surgery for sex reassignment

5.1 We recommend that transsexual persons consider genital sex reassignment surgery only after both the physician responsible for endocrine transition therapy and the MHP find surgery advisable. (1 ⊕○○○)

5.2 We recommend that genital sex reassignment surgery be recommended only after completion of at least 1 yr of consistent and compliant hormone treatment. (1 ⊕○○○)

5.3 We recommend that the physician responsible for endocrine treatment medically clear transsexual individuals for sex reassignment surgery and collaborate with the surgeon regarding hormone use during and after surgery. (1 ⊕○○○)

Introduction

Men and women have experienced the confusion and anguish resulting from rigid, forced conformity to sexual dimorphism throughout recorded history. Aspects

of gender variance have been part of biological, psychological, and sociological debates among humans in modern history. The 20th century marked the beginning of a social awakening for men and women “trapped” in the wrong body (1). Harry Benjamin and Magnus Hirschfeld, who met in 1907, pioneered the medical responses to those who sought relief from and resolution of their profound discomfort, enabling the “transsexual,” a term coined by Hirschfeld in 1923, to live a gender-appropriate life, occasionally facilitated by surgery (2).

Endocrine treatment of transsexual persons [note: In the current psychiatric classification system, the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (DSM-IV-TR), the term “gender identity disorder” is used instead of “transsexualism” (3)], previously limited to ineffective elixirs, creams, and implants, became reasonable with the availability of diethylstilbestrol in 1938 and after the isolation of testosterone in 1935. Personal stories of role models, treated with hormones and sex reassignment surgery, appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association (HBIGDA) was founded in September 1979; it is now known as the World Professional Association of Transgender Health (WPATH). The Association’s “Standards of Care” (SOC) was first published by HBIGDA in 1979, and its sixth edition is currently being revised. These carefully prepared documents have provided mental health and medical professionals with general guidelines for the evaluation and treatment of transsexual persons.

Before 1975, few peer-reviewed articles were published concerning endocrine treatment of transsexual persons. Since that time, more than 800 articles about various aspects of transsexual care have appeared. It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience, that will enable endocrinologists to provide safe and effective endocrine treatment for individuals diagnosed with GID or transsexualism by MHPs. In the future, rigorous evaluation of the effectiveness and safety of endocrine protocols is needed. What will be required is the careful assessment of: 1) the effects of prolonged delay of puberty on bone growth and development among adolescents; 2) in adults, the effects on outcome of both endogenous and cross-sex hormone levels during treatment; 3) the requirement for and the effects of antiandrogens and progestins during treatment; and 4) long-term medical and psychological risks of sex reassignment. These needs can be met only by a commitment of mental health and endocrine investigators to collaborate in long-term, large-scale studies across countries that employ the same diagnostic

and inclusion criteria, medications, assay methods, and response assessment tools.

Terminology and its use vary and continue to evolve. Table 1 contains definitions of terms as they are used throughout the Guideline.

TABLE 1. Definitions of terms used in this guideline

Sex refers to attributes that characterize biological maleness or femaleness; the best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics
<i>Gender identity</i> is used to describe a person’s fundamental sense of being a man, a woman, or of indeterminate sex.
<i>Gender identity disorder</i> (GID) is a DSM-IV-TR diagnosis. This psychiatric diagnosis is given when a strong and persistent cross-gender identification, combined with a persistent discomfort with one’s sex or sense of inappropriateness in the gender role of that sex, causes clinically significant distress.
<i>Gender role</i> is used to refer to behaviors, attitudes, and personality traits that a society, in a given culture and historical period, designates as masculine or feminine, that is, more “appropriate” to, or typical of, the social role as men or as women.
<i>Gender dysphoria</i> is the distress and unease experienced if gender identity and sex are not completely congruent.
<i>Sexual orientation</i> can be defined by a person’s relative responsiveness to sexual stimuli. The most salient dimension of sexual orientation is the sex of the person to whom one is attracted sexually; sexual orientation is not entirely similar to <i>sexual identity</i> ; a person may, for example, be predominantly aroused by homoerotic stimuli, yet not regard himself or herself to be gay or lesbian.
<i>Sex reassignment</i> refers to the complete treatment procedure for those who want to adapt their bodies to the desired sex.
<i>Sex reassignment surgery</i> refers only to the surgical part of this treatment.
<i>Transsexual</i> people identify as, or desire to live and be accepted as, a member of the gender opposite to that assigned at birth; the term <i>male-to-female</i> (MTF) <i>transsexual person</i> refers to a biological male who identifies as, or desires to be, a member of the female gender; <i>female-to-male</i> (FTM) <i>transsexual person</i> refers to a biological female who identifies as, or desires to be, a member of the male gender.
<i>Transition</i> refers to the period of time during which transsexual persons change their physical, social, and legal characteristics to the gender opposite that of their biological sex. Transition may also be regarded as an ongoing process of physical change and psychological adaptation.

Note: In this Guideline, we have chosen to use the term “transsexual” throughout as defined by the ICD-10 Diagnostic Code (see Table 3). We recognize that “transsexual” and “transgender” are terms often used interchangeably. However, because “transgender” may also be used to identify individuals whose gender identity does not conform to the conventional gender roles of either male or female and who may not seek endocrine treatment as described herein, we prefer to use “transsexual” as an adjective (e.g. when referring to persons, individuals, men, or women and, when appropriate, referring to subjects in research studies).

Etiology of Gender Identity Disorders

One's self-awareness as male or female evolves gradually during infant life and childhood. This process of cognitive and affective learning happens in interaction with parents, peers, and environment, and a fairly accurate timetable exists for the steps in this process (4). Normative psychological literature, however, does not address when gender identity becomes crystallized and what factors contribute to the development of an atypical gender identity. Factors that have been reported in clinical studies may well enhance or perpetuate rather than originate a GID (for an overview, see Ref. 5). Behavioral genetic studies suggest that, in children, atypical gender identity and role development has a heritable component (6, 7). Because, in most cases, GID does not persist into adolescence or adulthood, findings in children with GID cannot be extrapolated to adults.

In adults, psychological studies investigating etiology hardly exist. Studies that have investigated potential causal factors are retrospective and rely on self-report, making the results intrinsically unreliable.

Most attempts to identify biological underpinnings of gender identity in humans have investigated effects of sex steroids on the brain (functions) (for a review, see Ref. 8). Prenatal androgenization may predispose to development of a male gender identity. However, most 46,XY female-raised children with disorders of sex development and a history of prenatal androgen exposure do not develop a male gender identity (9, 10), whereas 46,XX subjects exposed to prenatal androgens show marked behavioral masculinization, but this does not necessarily lead to gender dysphoria (11–13). MTF transsexual individuals, with a male androgen exposure prenatally, develop a female gender identity through unknown mechanisms, apparently overriding the effects of prenatal androgens. There is no comprehensive understanding of hormonal imprinting on gender identity formation. It is of note that, in addition to hormonal factors, genetic mechanisms may bear on psychosexual differentiation (14).

Maternal immunization against the H-Y antigen has been proposed (15, 16). This hypothesis states that the repeatedly reported fraternal birth order effect reflects the progressive immunization of some mothers to Y-linked minor histocompatibility antigens (H-Y antigens) by each succeeding male fetus and the increasing effects of such immunization on the future sexual orientation of each succeeding male fetus. Sibling sex ratio studies have not been experimentally supported (17).

Studies have also failed to find differences in circulating levels of sex steroids between transsexual and nontranssexual individuals (18).

In summary, neither biological nor psychological studies provide a satisfactory explanation for the intriguing phenomenon of GIDs. In both disciplines, studies have been able to correlate certain findings to GIDs, but the findings are not robust and cannot be generalized to the whole population.

Method of Development of Evidence-based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of The Endocrine Society deemed the diagnosis and treatment of transsexual individuals a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in development and implementation of evidence-based guidelines (19). A detailed description of the grading scheme has been published elsewhere (20). The Task Force used the best available research evidence that Task Force members identified and two commissioned systematic reviews (21, 22) to develop some of the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕○○○ denotes very low quality evidence, ⊕⊕○○ denotes low quality, ⊕⊕⊕○ denotes moderate quality, and ⊕⊕⊕⊕ denotes high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each “recommendation” is a description of the “evidence” and the “values” that panelists considered in making the recommendation; in some instances, there are “remarks,” a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions. Some statements in this guideline (1.3 and 1.4) are not graded. These are statements the task force felt it was necessary to make, and it considers them matters about which no sensible health-

care professional could possibly consider advocating the contrary (e.g. clinicians should conduct an adequate history taking and physical examination, clinicians should educate patients about their condition). These statements have not been subject to structured review of the evidence and are thus not graded.

1.0 Diagnostic procedure

Sex reassignment is a multidisciplinary treatment. It requires five processes: diagnostic assessment, psychotherapy or counseling, RLE, hormone therapy, and surgical therapy. The focus of this Guideline is hormone therapy, although collaboration with appropriate professionals responsible for each process maximizes a successful outcome. It would be ideal if care could be given by a multidisciplinary team at one treatment center, but this is not always possible. It is essential that all caregivers be aware of and understand the contributions of each discipline and that they communicate throughout the process.

Diagnostic assessment and psychotherapy

Because GID may be accompanied with psychological or psychiatric problems (see Refs. 23–27), it is necessary that the clinician making the GID diagnosis be able 1) to make a distinction between GID and conditions that have similar features; 2) to diagnose accurately psychiatric conditions; and 3) to undertake appropriate treatment thereof. Therefore, the SOC guidelines of the WPATH recommend that the diagnosis be made by a MHP (28). For children and adolescents, the MHP should also have training in child and adolescent developmental psychopathology.

MHPs usually follow the WPATH's SOC. The main aspects of the diagnostic and psychosocial counseling are described below, and evidence supporting the SOC guidelines is given, whenever available.

During the diagnostic procedure, the MHP obtains information from the applicants for sex reassignment and, in the case of adolescents, the parents or guardians regarding various aspects of their general and psychosexual development and current functioning. On the basis of this information the MHP:

- decides whether the applicant fulfills DSM-IV-TR or ICD-10 criteria (see Tables 2 and 3) for GID;
- informs the applicant about the possibilities and limitations of sex reassignment and other kinds of treatment to prevent unrealistically high expectations; and
- assesses potential psychological and social risk factors for unfavorable outcomes of medical interventions.

In cases in which severe psychopathology or circumstances, or both, seriously interfere with the diagnostic work or make

TABLE 2. DSM-IV-TR diagnostic criteria for GID (3)

- A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex).
In children, the disturbance is manifested by four (or more) of the following:
 1. Repeatedly stated desire to be, or insistence that he or she is, the other sex.
 2. In boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing.
 3. Strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex.
 4. Intense desire to participate in the stereotypical games and pastimes of the other sex.
 5. Strong preference for playmates of the other sex.

In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex.
 - Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex.
In children, the disturbance is manifested by any of the following:
 1. In boys, assertion that his penis or testes is disgusting or will disappear, or assertion that it would be better not to have a penis, or aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities.
 2. In girls, rejection of urinating in a sitting position, assertion that she has or will grow a penis, assertion that she does not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing.

In adolescents and adults, the disturbance is manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g. request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex.
 - The disturbance is not concurrent with a physical intersex condition.
 - The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Codes based on current age:
302.6 GID in children
302.85 GID in adolescents or adults
- Specify whether (for sexually mature individuals):
Sexually attracted to males
Sexually attracted to females
Sexually attracted to both
Sexually attracted to neither

satisfactory treatment unlikely, management of the other issues should be addressed first. Literature on postoperative regret suggests that severe psychiatric comorbidity and lack of support may interfere with good outcome (30–33).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (34) and,

TABLE 3. ICD-10 criteria for transsexualism and GID of childhood (29)

Transsexualism (F64.0) criteria:

1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 yr.
3. The disorder is not a symptom of another mental disorder or a genetic, intersex, or chromosomal abnormality.

GID of childhood (F64.2) has separate criteria for girls and for boys.

Criteria for girls:

1. The individual shows persistent and intense distress about being a girl and has a stated desire to be a boy (not merely a desire for any perceived cultural advantages of being a boy) or insists that she is a boy.
2. Either of the following must be present:
 - a. Persistent marked aversion to normative feminine clothing and insistence on wearing stereotypical masculine clothing.
 - b. Persistent repudiation of female anatomical structures, as evidenced by at least one of the following:
 - i. An assertion that she has, or will grow, a penis.
 - ii. Rejection of urination in a sitting position.
 - iii. Assertion that she does not want to grow breasts or menstruate.
3. The girl has not yet reached puberty.
4. The disorder must have been present for at least 6 months.

Criteria for boys:

1. The individual shows persistent and intense distress about being a boy and has a desire to be a girl or, more rarely, insists that he is a girl.
2. Either of the following must be present:
 - a. Preoccupation with stereotypic female activities, as shown by a preference for either cross-dressing or simulating female attire or by an intense desire to participate in the games and pastimes of girls and rejection of stereotypical male toys, games, and activities.
 - b. Persistent repudiation of male anatomical structures, as evidenced by at least one of the following repeated assertions:
 - i. That he will grow up to become a woman (not merely in the role).
 - ii. That his penis or testes are disgusting or will disappear.
 - iii. That it would be better not to have a penis or testes.
3. The boy has not reached puberty.
4. The disorder must have been present for at least 6 months.

preferably, a child psychiatric evaluation (by a clinician other than the diagnostician). Di Ceglie *et al.* (35) showed that 75% of the adolescents referred to their Gender Identity clinic in the United Kingdom reported relationship problems with parents. Therefore, a family evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic procedure.

The real-life experience

WPATH's SOC states that "the act of fully adopting a new or evolving gender role or gender presentation in everyday life is known as the real-life experience. The real-life experience is essential to the transition to the gender role that is congruent with the patient's gender identity. The real-life experience tests the person's resolve, the capacity to function in the preferred gender, and the adequacy of social, economic, and psychological supports. It assists both the patient and the MHP in their judgments about how to proceed" (28). During the RLE, the person should fully experience life in the desired gender role before irreversible physical treatment is undertaken. Living 12 months full-time in the desired gender role is recommended (28). Testing an applicant's ability to function in the desired gender assists the applicant, the MHP and the endocrinologist in their judgements about how to proceed. During the RLE, the person's feeling about the social transformation, including coping with the responses of others, is a major

focus of the counseling. Applicants increasingly start the RLE long before they are referred for hormone treatment.

Eligibility and readiness criteria

The WPATH SOC document requires that both adolescents and adults applying for hormone treatment and surgery satisfy two sets of criteria — eligibility and readiness — before proceeding (28). There are eligibility and readiness criteria for hormone therapy for adults (Table 4) and eligibility cri-

TABLE 4. Hormone therapy for adults

Adults are **eligible** for cross-sex hormone treatment if they (28):

1. Fulfill DSM IV-TR or ICD-10 criteria for GID or transsexualism (see Tables 2 and 3).
2. Do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment.
3. Demonstrate knowledge and understanding of the expected outcomes of hormone treatment, as well as the medical and social risks and benefits; AND
4. Have experienced a documented RLE of at least 3-month duration OR had a period of psychotherapy (duration specified by the MHP after the initial evaluation, usually a minimum of 3 months).

Adults should fulfill the following **readiness criteria** before the cross-sex hormone treatment. The applicant:

1. Has had further consolidation of gender identity during a RLE or psychotherapy.
2. Has made some progress in mastering other identified problems leading to improvement or continuing stable mental health.
3. Is likely to take hormones in a responsible manner.

TABLE 5. Hormone therapy for adolescents

Adolescents are eligible and ready for GnRH treatment if they:
1. Fulfill DSM IV-TR or ICD-10 criteria for GID or transsexualism.
2. Have experienced puberty to at least Tanner stage 2.
3. Have (early) pubertal changes that have resulted in an increase of their gender dysphoria.
4. Do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment.
5. Have adequate psychological and social support during treatment, AND
6. Demonstrate knowledge and understanding of the expected outcomes of GnRH analog treatment, cross-sex hormone treatment, and sex reassignment surgery, as well as the medical and the social risks and benefits of sex reassignment.
Adolescents are eligible for cross-sex hormone treatment if they:
1. Fulfill the criteria for GnRH treatment, AND
2. Are 16 yr or older.

Readiness criteria for adolescents eligible for cross-sex hormone treatment are the same as those for adults.

teria for adolescents (Table 5). Eligibility and readiness criteria for sex reassignment surgery in adults and adolescents are the same (see Section 5.0). Although the eligibility criteria have not been evaluated in formal studies, a few follow-up studies on adolescents who fulfilled these criteria and had started cross-sex hormone treatment from the age of 16 indicate good postoperative results (36–38).

One study on MTF transsexual subjects reports that outcome was not associated with minimum eligibility requirements of the WPATH's SOC. However, this study was performed among a group of individuals with a relatively high socioeconomic background (39). One study investigating the need for psychotherapy for sex-reassignment applicants, based on questionnaire scores, suggests that "classical" forms of psychotherapy before medical interventions are not needed in about two thirds of the applicants (40).

Recommendations for those involved in the hormone treatment of applicants for sex reassignment

1.1 Recommendation

We recommend that the diagnosis of GID be made by a MHP. For children and adolescents, the MHP must also have training in child and adolescent developmental psychopathology. (1 ⊕⊕○○)

1.1 Evidence

GID may be accompanied with psychological or psychiatric problems (see Refs. 23–27). It is therefore necessary that the clinician making the GID diagnosis be able to make a distinction between GID and conditions that have similar features, to accurately diagnose psychiatric con-

ditions, and to ensure that any such conditions are treated appropriately. One condition with similar features is body dysmorphic disorder or Skoptic syndrome, a condition in which a person is preoccupied with or engages in genital self-mutilation, such as castration, penectomy, or clitoridectomy (41).

1.1 Values and Preferences

The Task Force placed a very high value on avoiding harm from hormone treatment to individuals who have conditions other than GID and who may not be ready for the physical changes associated with this treatment, and it placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the strong recommendation in the face of low-quality evidence.

1.2 Recommendation

Given the high rate of remission of GID after the onset of puberty, we recommend against a complete social role change and hormone treatment in prepubertal children with GID. (1 ⊕⊕○○)

1.2 Evidence

In most children with GID, the GID does not persist into adolescence. The percentages differ between studies, probably dependent upon which version of the DSM was used in childhood, ages of children, and perhaps culture factors. However, the large majority (75–80%) of prepubertal children with a diagnosis of GID in childhood do not turn out to be transsexual in adolescence (42–44); for a review of seven older studies see Ref. 45. Clinical experience suggests that GID can be reliably assessed only after the first signs of puberty.

This recommendation, however, does not imply that children should be entirely denied to show cross-gender behaviors or should be punished for exhibiting such behaviors.

1.2 Values and Preferences

This recommendation places a high value on avoiding harm with hormone therapy in prepubertal children who may have GID that will remit after the onset of puberty and places a relatively lower value on foregoing the potential benefits of early physical sex change induced by hormone therapy in prepubertal children with GID. This justifies the strong recommendation in the face of very low quality evidence.

1.3 Recommendation

We recommend that physicians evaluate and ensure that applicants understand the reversible and irreversible effects of hormone suppression (e.g. GnRH analog treat-

ment) and of cross-sex hormone treatment before they start hormone treatment.

1.3 Remarks

In all treatment protocols, compliance and outcome are enhanced by clear expectations concerning the effects of the treatment. The lengthy diagnostic procedure (GnRH analog treatment included, because this reversible treatment is considered to be a diagnostic aid) and long duration of the period between the start of the hormone treatment and sex reassignment surgery give the applicant ample opportunity to make balanced decisions about the various medical interventions. Clinical evidence shows that applicants react in a variety of ways to this treatment phase. The consequences of the social role change are sometimes difficult to handle, increasing understanding of treatment aspects may be frightening, and a change in gender dysphoric feelings may lead to confusion. Significant adverse effects on mental health can be prevented by a clear understanding of the changes that will occur and the time course of these changes.

1.4 Recommendation

We recommend that all transsexual individuals be informed and counseled regarding options for fertility before initiation of puberty suppression in adolescents and before treatment with sex hormones of the desired sex in both adolescents and adults.

1.4 Remarks

Persons considering hormone use for sex reassignment need adequate information about sex reassignment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision about this treatment. Because early adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormones, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding future fertility of adolescents or adults beginning sex reassignment treatment.

Prolonged pubertal suppression using GnRH analogs is reversible and should not prevent resumption of pubertal development upon cessation of treatment. Although sperm production and development of the reproductive tract in early adolescent biological males with GID are insufficient for cryopreservation of sperm, they should be counseled that sperm production can be initiated after prolonged gonadotropin suppression, before estrogen treatment. This sperm production can be accomplished by

spontaneous gonadotropin (both LH and FSH) recovery after cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production. It should be noted that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6–12 months of gonadotropin treatment, although sperm numbers at the time of pregnancy in these patients are far below the normal range (46, 47).

Girls can expect no adverse effects when treated with pubertal suppression. They should be informed that no data are available regarding timing of spontaneous ovulation or response to ovulation induction after prolonged gonadotropin suppression.

All referred subjects who satisfy eligibility and readiness criteria for endocrine treatment, at age 16 or as adults, should be counseled regarding the effects of hormone treatment on fertility and available options that may enhance the chances of future fertility, if desired (48, 49). The occurrence and timing of potentially irreversible effects should be emphasized. Cryopreservation of sperm is readily available, and techniques for cryopreservation of oocytes, embryos, and ovarian tissue are being improved (50).

In biological males, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. Prolonged exposure of the testes to estrogen has been associated with testicular damage (51–53). Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In biological females, the effect of prolonged treatment with exogenous testosterone upon ovarian function is uncertain. Reports of an increased incidence of polycystic ovaries in FTM transsexual persons, both before and as a result of androgen treatment, should be acknowledged (54, 55). Pregnancy has been reported in FTM transsexual persons who have had prolonged androgen treatment, but no genital surgery (56). Counsel from a gynecologist before hormone treatment regarding potential fertility preservation after oophorectomy will clarify available and future options (57).

2.0 Treatment of adolescents

Over the past decade, clinicians have progressively acknowledged the suffering of young transsexual adolescents that is caused by their pubertal development. Indeed, an adolescent with GID often considers the pubertal physical changes to be unbearable. Because early medical intervention may prevent this psychological harm, various clinics have decided to start treating young adolescents

with GID with puberty-suppressing medication (a GnRH analog). As compared with starting sex reassignment long after the first phases of puberty, a benefit of pubertal suppression is relief of gender dysphoria and a better psychological and physical outcome.

The physical changes of pubertal development are the result of maturation of the hypothalamo-pituitary-gonadal axis and development of the secondary sex characteristics. Gonadotropin secretion increases with a day-night rhythm with higher levels of LH during the night. The nighttime LH increase in boys is associated with a parallel testosterone increase. Girls do not show a day-night rhythm, although in early puberty, the highest estrogen levels are observed during the morning as a result of a delayed response by the ovaries (58).

In girls the first physical sign of the beginning of puberty is the start of budding of the breasts, followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, with menarche occurring approximately 2 yr later. In boys the first physical change is testicular growth. A testicular volume equal to or above 4 ml is seen as the first pubertal increase. From a testicular volume of 10 ml, daytime testosterone levels increase, leading to virilization (59).

2.1–2.2 Recommendations

2.1 We recommend that adolescents who fulfill eligibility and readiness criteria for gender reassignment initially undergo treatment to suppress pubertal development. (1 ⊕○○○)

2.2 We recommend that suppression of pubertal hormones start when girls and boys first exhibit physical changes of puberty (confirmed by pubertal levels of estradiol and testosterone, respectively), but no earlier than Tanner stages 2–3. (1 ⊕○○○)

2.1–2.2 Evidence

Pubertal suppression aids in the diagnostic and therapeutic phase, in a manner similar to the RLE (60, 61). Management of gender dysphoria usually improves. In addition, the hormonal changes are fully reversible, enabling full pubertal development in the biological gender if appropriate. Therefore, we advise starting suppression of puberty before irreversible development of sex characteristics.

The experience of full biological puberty, an undesirable condition, may seriously interfere with healthy psychological functioning and well-being. Suffering from gender dysphoria without being able to present socially in the desired social role or to stop the development of secondary sex characteristics may result in an arrest in emotional, social, or intellectual development.

Another reason to start sex reassignment early is that the physical outcome after intervention in adulthood is far

less satisfactory than intervention at age 16 (36, 38). Looking like a man (woman) when living as a woman (man) creates difficult barriers with enormous lifelong disadvantages.

Pubertal suppression maintains end-organ sensitivity to sex steroids observed during early puberty, enabling satisfactory cross-sex body changes with low doses and avoiding irreversible characteristics that occur by midpuberty.

The protocol of suppression of pubertal development can also be applied to adolescents in later pubertal stages. In contrast to effects in early pubertal adolescents, physical sex characteristics, such as breast development in girls and lowering of the voice and outgrowth of the jaw and brow in boys, will not regress completely.

Unlike the developmental problems observed with delayed puberty, this protocol requires a MHP skilled in child and adolescent psychology to evaluate the response of the adolescent with GID after pubertal suppression. Adolescents with GID should experience the first changes of their biological, spontaneous puberty because their emotional reaction to these first physical changes has diagnostic value. Treatment in early puberty risks limited growth of the penis and scrotum that may make the surgical creation of a vagina from scrotal tissue more difficult.

2.1–2.2 Values and Preferences

These recommendations place a high value on avoiding the increasing likelihood of an unsatisfactory physical change when secondary sexual characteristics have become manifest and irreversible, as well as a high value on offering the adolescent the experience of the desired gender. These recommendations place a lower value on avoiding potential harm from early hormone therapy.

2.1–2.2 Remarks

Tanner stages of breast and male genital development are given in Table 6. Blood levels of sex steroids during Tanner stages of pubertal development are given in Table 7. Careful documentation of hallmarks of pubertal development will ensure precise timing of initiation of pubertal suppression.

Irreversible and, for transsexual adolescents, undesirable sex characteristics in female puberty are large breasts and short stature and in male puberty are Adam's apple; low voice; male bone configuration such as large jaws, big feet, and hands; tall stature; and male hair pattern on the face and extremities.

2.3 Recommendation

We recommend that GnRH analogs be used to achieve suppression of pubertal hormones. (1 ⊕⊕○○)

TABLE 6. Description of tanner stages of breast development and male external genitalia

For breast development:

1. Preadolescent.
2. Breast and papilla elevated as small mound; areolar diameter increased.
3. Breast and areola enlarged, no contour separation.
4. Areola and papilla form secondary mound.
5. Mature; nipple projects, areola part of general breast contour.

For penis and testes:

1. Preadolescent.
2. Slight enlargement of penis; enlarged scrotum, pink texture altered.
3. Penis longer, testes larger.
4. Penis larger, glans and breadth increase in size; testes larger, scrotum dark.
5. Penis and testes adult size.

Adapted from Ref. 62.

2.3 Evidence

Suppression of pubertal development and gonadal function is accomplished most effectively by gonadotropin suppression with GnRH analogs and antagonists. Analogs suppress gonadotropins after a short period of stimulation, whereas antagonists immediately suppress pituitary secretion (64, 65). Because no long-acting antagonists are available for use as pharmacotherapy, long-acting analogs are the currently preferred treatment option.

During treatment with the GnRH analogs, slight development of sex characteristics will regress and, in a later phase of pubertal development, will be halted. In girls, breast development will become atrophic, and menses will stop; in boys, virilization will stop, and testicular volume will decrease (61).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploring of his/

her reassignment wish, the applicant no longer desires sex reassignment, pubertal suppression can be discontinued. Spontaneous pubertal development will resume immediately (66).

Men with delayed puberty have decreased BMD. Treatment of adults with GnRH analogs results in loss of BMD (67). In children with central precocious puberty, bone density is relatively high for age. Suppressing puberty in these children using GnRH analogs will result in a further increase in BMD and stabilization of BMD SD scores (68). Initial data in transsexual subjects demonstrate no change of bone density during GnRH analog therapy (61). With cross-hormone treatment, bone density increases. The long-term effects on bone density and peak bone mass are being evaluated.

GnRH analogs are expensive and not always reimbursed by insurance companies. Although there is no clinical experience in this population, financial considerations may require treatment with progestins as a less effective alternative. They suppress gonadotropin secretion and exert a mild peripheral antiandrogen effect in boys. Depomedroxyprogesterone will suppress ovulation and progesterone production for long periods of time, although residual estrogen levels vary. In high doses, progestins are relatively effective in suppression of menstrual cycling in girls and women and androgen levels in boys and men. However, at these doses, side effects such as suppression of adrenal function and suppression of bone growth may occur (69). Antiestrogens in girls and antiandrogens in boys can be used to delay the progression of puberty (70, 71). Their efficacy, however, is far less than that of the GnRH analogs.

2.3 Values and Preferences

For persons who can afford the therapy, our recommendation of GnRH analogs places a higher value on the superior efficacy, safety, and reversibility of the pubertal hormone suppression achieved, as compared with the alternatives, and a relatively lower value on limiting the cost of therapy. Of the available alternatives, a depot progestin preparation may be partially effective, but it is not as safe (69, 72); its lower cost may make it an acceptable treatment for persons who cannot afford GnRH.

2.3 Remarks

Measurements of gonadotropin and sex steroid levels give precise information about suppression of the gonadal axis. If the gonadal axis is not completely suppressed, the interval of GnRH analog injections should be shortened. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone accretion. The clinical protocol to be used is shown in Table 8.

TABLE 7. Estradiol levels in female puberty and testosterone levels in male puberty during night and day

Tanner stage	Nocturnal	Diurnal
Estradiol (pmol/liter) ^a		
B1	<37	<37
B2	38.5	56.3
B3	81.7	107.3
B4	162.9	132.3
B5	201.6	196.7
Testosterone (nmol/liter) ^b		
G1	<0.25	<0.25
G2	1.16	0.54
G3	3.76	0.62
G4	9.83	1.99
G5	13.2	7.80
Adult	18.8	17.0

Data represent median of hourly measurements from 2400–0600 h (nocturnal) and 1200–1800 h (diurnal).

^a Adapted from Ref. 63.

^b Adapted from Ref. 59.

TABLE 8. Follow-up protocol during suppression of puberty

Every 3 months
Anthropometry: height, weight, sitting height, Tanner stages
Laboratory: LH, FSH, estradiol/testosterone
Every year
Laboratory: renal and liver function, lipids, glucose, insulin, glycosylated hemoglobin
Bone density using dual-energy x-ray absorptiometry
Bone age on x-ray of the left hand

Glucose and lipid metabolism, complete blood counts, and liver and renal function should be monitored during suppression and cross-sex hormone substitution. For the evaluation of growth, anthropometric measurements are informative. To assess bone density, dual energy x-ray absorptiometry scans can be performed.

2.4 Recommendation

We suggest that pubertal development of the desired, opposite sex be initiated at the age of 16 yr, using a gradually increasing dose schedule of cross-sex steroids. (2 ⊕○○○)

2.4 Evidence

In many countries, 16-yr-olds are legal adults with regard to medical decision making. This is probably because, at this age, most adolescents are able to make complex cognitive decisions. Although parental consent may not be required, obtaining it is preferred because the support of parents should improve the outcome during this complex phase of the adolescent's life (61).

For the induction of puberty, we use a similar dose scheme of induction of puberty in these hypogonadal transsexual adolescents as in other hypogonadal individuals (Table 9). We do not advise the use of sex steroid creams or patches because there is little experience for induction of puberty. The transsexual adolescent is hypogonadal and may be sensitive to high doses of cross-sex steroids, causing adverse effects of striae and abnormal breast shape in girls and cystic acne in boys.

In FTM transsexual adolescents, suppression of puberty may halt the growth spurt. To achieve maximum height, slow introduction of androgens will mimic a "pubertal" growth spurt. If the patient is relatively short, one may treat with oxandrolone, a growth-stimulating anabolic steroid also successfully applied in women with Turner syndrome (73–75).

In MTF transsexual adolescents, extreme tall stature is often a genetic probability. The estrogen dose may be increased by more rapid increments in the schedule. Estrogens may be started before the age of 16 (in exceptional cases), or estrogens can be prescribed in growth-inhibiting doses (61).

TABLE 9. Protocol induction of puberty

Induction of female puberty with oral 17-β estradiol, increasing the dose every 6 months:
5 μg/kg/d
10 μg/kg/d
15 μg/kg/d
20 μg/kg/d
Adult dose = 2 mg/d
Induction of male puberty with intramuscular testosterone esters, increasing the dose every 6 months:
25 mg/m ² per 2 wk im
50 mg/m ² per 2 wk im
75 mg/m ² per 2 wk im
100 mg/m ² per 2 wk im

We suggest that treatment with GnRH analogs be continued during treatment with cross-sex steroids to maintain full suppression of pituitary gonadotropin levels and, thereby, gonadal steroids. When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion (Table 7). The estrogen doses used may result in reactivation of gonadotropin secretion and endogenous production of testosterone that can interfere with the effectiveness of the treatment. GnRH analog treatment is advised until gonadectomy.

2.4 Values and Preferences

Identifying an age at which pubertal development is initiated will be by necessity arbitrary, but the goal is to start this process at a time when the individual will be able to make informed mature decisions and engage in the therapy, while at the same time developing along with his or her peers. Growth targets reflect personal preferences, often shaped by societal expectations. Individual preferences should be the key determinant, rather than the professional's deciding *a priori* that MTF transsexuals should be shorter than FTM transsexuals.

2.4 Remarks

Protocols for induction of puberty can be found in Table 9.

We recommend monitoring clinical pubertal development as well as laboratory parameters (Table 10). Sex

TABLE 10. Follow-up protocol during induction of puberty

Every 3 months
Anthropometry: height, weight, sitting height, Tanner stages
Laboratory: endocrinology, LH, FSH, estradiol/testosterone
Every year
Laboratory: renal and liver function, lipids, glucose, insulin, glycosylated hemoglobin
Bone density using dual-energy x-ray absorptiometry
Bone age on x-ray of the left hand

These parameters should also be measured at long term. For bone development, they should be measured until the age of 25–30 yr or until peak bone mass has been reached.

steroids of the desired sex will initiate pubertal development, which can be (partially) monitored using Tanner stages. In addition, the sex steroids will affect growth and bone development, as well as insulin sensitivity and lipid metabolism, as in normal puberty (76, 77).

2.5–2.6 Recommendations

2.5 We recommend referring hormone-treated adolescents for surgery when 1) the RLE has resulted in a satisfactory social role change, 2) the individual is satisfied about the hormonal effects, and 3) the individual desires definitive surgical changes. (1 ⊕○○○)

2.6 We suggest deferring for surgery until the individual is at least 18 yr old. (2 ⊕○○○)

2.5–2.6 Evidence

Surgery is an irreversible intervention. The WPATH SOC (28) emphasizes that the “threshold of 18 should be seen as an eligibility criterion and not an indication in itself for active intervention.” If the RLE supported by sex hormones of the desired sex has not resulted in a satisfactory social role change, if the person is not satisfied with or is ambivalent about the hormonal effects, or if the person is ambivalent about surgery, then the applicant should not be referred for surgery (78, 79).

3.0 Hormonal therapy for transsexual adults

The two major goals of hormonal therapy are: 1) to reduce endogenous hormone levels and, thereby, the secondary sex characteristics of the individual’s biological (genetic) sex and assigned gender; and 2) to replace endogenous sex hormone levels with those of the reassigned sex by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with cross-sex hormones is codetermined in collaboration with both the person pursuing sex change and the MHP who made the diagnosis, performed psychological evaluation, and recommended sex reassignment. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being.

3.1–3.3 Recommendations

3.1 We recommend that treating endocrinologists confirm the diagnostic criteria of GID or transsexualism and the eligibility and readiness criteria for the endocrine phase of gender transition. (1 ⊕⊕⊕○)

3.2 We recommend that medical conditions that can be exacerbated by hormone depletion and cross-sex hormone treatment be evaluated and addressed before initiation of treatment (Table 11). (1 ⊕⊕⊕○)

TABLE 11. Medical conditions that can be exacerbated by cross-sex hormone therapy

Transsexual female (MTF): estrogen
Very high risk of serious adverse outcomes
Thromboembolic disease
Moderate to high risk of adverse outcomes
Macroprolactinoma
Severe liver dysfunction (transaminases >3 × upper limit of normal)
Breast cancer
Coronary artery disease
Cerebrovascular disease
Severe migraine headaches
Transsexual male (FTM): testosterone
Very high risk of serious adverse outcomes
Breast or uterine cancer
Erythrocytosis (hematocrit >50%)
Moderate to high risk of adverse outcomes
Severe liver dysfunction (transaminases >3 × upper limit of normal)

3.3 We suggest that cross-sex hormone levels be maintained in the normal physiological range for the desired gender. (2 ⊕⊕○○)

3.1–3.3 Evidence

Although the diagnosis of GID or transsexualism is made by an MHP, the referral for endocrine treatment implies fulfillment of the eligibility and readiness criteria (see *Section 1*) (28). It is the responsibility of the physician to whom the transsexual person has been referred to confirm that the person fulfills these criteria for treatment. This task can be accomplished by the physician’s becoming familiar with the terms and criteria presented in Tables 1–5, taking a thorough history from the person recommended for treatment, and discussing these criteria with the MHP. Continued evaluation of the transsexual person by the MHP, in collaboration with the treating endocrinologist, will ensure that the desire for sex change is appropriate, that the consequences, risks, and benefits of treatment are well understood, and that the desire for sex change persists.

FTM transsexual persons

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in FTM transsexual persons (80–84). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (85). Either parenteral or transdermal preparations can be used to achieve testosterone values in the normal male range (320–1000 ng/dl) (Table 12). Sustained supraphysiological levels of testosterone increase the risk of adverse reactions (see *Section 4.0*).

Similar to androgen therapy in hypogonadal men, testosterone treatment in the FTM individual results in increased

TABLE 12. Hormone regimens in the transsexual persons

	Dosage
MTF transsexual persons ^a	
Estrogen	
Oral: estradiol	2.0–6.0 mg/d
Transdermal: estradiol patch	0.1–0.4 mg twice weekly
Parenteral: estradiol valerate or cypionate	5–20 mg im every 2 wk 2–10 mg im every week
Antiandrogens	
Spironolactone	100–200 mg/d
Cyproterone acetate ^b	50–100 mg/d
GnRH agonist	3.75 mg sc monthly
FTM transsexual persons	
Testosterone	
Oral: testosterone undecanoate ^b	160–240 mg/d
Parenteral	
Testosterone enanthate or cypionate	100–200 mg im every 2 wk or 50% weekly
Testosterone undecanoate ^{b,c}	1000 mg every 12 wk
Transdermal	
Testosterone gel 1%	2.5–10 g/d
Testosterone patch	2.5–7.5 mg/d

^a Estrogens used with or without antiandrogens or GnRH agonist.

^b Not available in the United States.

^c 1000 mg initially, followed by an injection at 6 wk, then at 12-wk intervals.

muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness, and increased libido (86). Specific to the FTM transsexual person, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, and, usually, cessation of menses. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, addition of a progestational agent or endometrial ablation may be considered (87, 88). GnRH analogs or depot medroxyprogesterone may also be used to stop menses before testosterone treatment and to reduce estrogens to levels found in biological males.

MTF transsexual persons

The hormone regimen for MTF transsexual individuals is more complex than the FTM regimen. Most published clinical studies report the use of an antiandrogen in conjunction with an estrogen (80, 82–84, 89).

The antiandrogens shown to be effective reduce endogenous testosterone levels, ideally to levels found in adult biological women, to enable estrogen therapy to have its fullest effect. Two categories of these medications are progestins with antiandrogen activity and GnRH agonists (90). Spironolactone has antiandrogen properties by di-

rectly inhibiting testosterone secretion and by inhibiting androgen binding to the androgen receptor (83, 84). It may also have estrogenic activity (91). Cyproterone acetate, a progestational compound with antiandrogenic properties (80, 82), is widely used in Europe. Flutamide blocks binding of androgens to the androgen receptor, but it does not lower serum testosterone levels; it has liver toxicity, and its efficacy has not been demonstrated.

Dittrich (90), reporting on a series of 60 MTF transsexual persons who used monthly the GnRH agonist goserelin acetate in combination with estrogen, found this regimen to be effective in reducing testosterone levels with low incidence of adverse reactions.

Estrogen can be given orally as conjugated estrogens, or 17 β -estradiol, as transdermal estrogen, or parenteral estrogen esters (Table 12).

Measurement of serum estradiol levels can be used to monitor oral, transdermal, and im estradiol or its esters. Use of conjugated estrogens or synthetic estrogens cannot be monitored by blood tests. Serum estradiol should be maintained at the mean daily level for premenopausal women (<200 pg/ml), and the serum testosterone level should be in the female range (<55 ng/dl). The transdermal preparations may confer an advantage in the older transsexual women who may be at higher risk for thromboembolic disease (92).

Venous thromboembolism may be a serious complication. A 20-fold increase in venous thromboembolic disease was reported in a large cohort of Dutch transsexual subjects (93). This increase may have been associated with the use of ethinyl estradiol (92). The incidence decreased upon cessation of the administration of ethinyl estradiol (93). Thus, the use of synthetic estrogens, especially ethinyl estradiol, is undesirable because of the inability to regulate dose by measurement of serum levels and the risk of thromboembolic disease. Deep vein thrombosis occurred in 1 of 60 MTF transsexual persons treated with a GnRH analog and oral estradiol (90). The patient was found to have a homozygous C677 T mutation. Administration of cross-sex hormones to 162 MTF and 89 FTM transsexual persons was not associated with venous thromboembolism despite an 8.0 and 5.6% incidence of thrombophilia, respectively (94). Thrombophilia screening of transsexual persons initiating hormone treatment should be restricted to those with a personal or family history of venous thromboembolism (94). Monitoring D-dimer levels during treatment is not recommended (95).

3.1–3.3 Values and Preferences

Our recommendation to maintain levels of cross-sex hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharma-

colological doses. Those receiving endocrine treatment who have relative contraindications to hormones (*e.g.* persons who smoke, have diabetes, have liver disease, *etc.*) should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

3.1–3.3 Remarks

All endocrine-treated individuals should be informed of all risks and benefits of cross-sex hormones before initiation of therapy. Cessation of tobacco use should be strongly encouraged in MTF transsexual persons to avoid increased risk of thromboembolism and cardiovascular complications.

3.4 Recommendation

We suggest that endocrinologists review with persons treated the onset and time course of physical changes induced by cross-sex hormone treatment. (2 ⊕⊕○○)

3.4 Evidence

FTM transsexual persons

Physical changes that are expected to occur during the first 3 months of initiation of testosterone therapy include cessation of menses, increased libido, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice, clitoromegaly, and, in some individuals, male pattern hair loss (83, 96, 97) (Table 13).

MTF transsexual persons

Physical changes that may occur in the first 3–6 months of estrogen and antiandrogen therapy include decreased libido, decreased facial and body hair, decreased oiliness of skin, breast tissue growth, and redistribution of fat mass (82, 83, 84, 96, 97) (Table 14). Breast development is

TABLE 13. Masculinizing effects in FTM transsexual persons

Effect	Onset (months) ^a	Maximum (yr) ^a
Skin oiliness/acne	1–6	1–2
Facial/body hair growth	6–12	4–5
Scalp hair loss	6–12	^b
Increased muscle mass/strength	6–12	2–5
Fat redistribution	1–6	2–5
Cessation of menses	2–6	^c
Clitoral enlargement	3–6	1–2
Vaginal atrophy	3–6	1–2
Deepening of voice	6–12	1–2

^a Estimates represent clinical observations. See Refs. 81, 92, and 93.

^b Prevention and treatment as recommended for biological men.

^c Menorrhagia requires diagnosis and treatment by a gynecologist.

TABLE 14. Feminizing effects in MTF transsexual persons

Effect	Onset ^a	Maximum ^a
Redistribution of body fat	3–6 months	2–3 yr
Decrease in muscle mass and strength	3–6 months	1–2 yr
Softening of skin/decreased oiliness	3–6 months	Unknown
Decreased libido	1–3 months	3–6 months
Decreased spontaneous erections	1–3 months	3–6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 months	2–3 yr
Decreased testicular volume	3–6 months	2–3 yr
Decreased sperm production	Unknown	>3 yr
Decreased terminal hair growth	6–12 months	>3 yr ^b
Scalp hair	No regrowth	^c
Voice changes	None	^d

^a Estimates represent clinical observations. See Refs. 81, 92, and 93.

^b Complete removal of male sexual hair requires electrolysis, or laser treatment, or both.

^c Familial scalp hair loss may occur if estrogens are stopped.

^d Treatment by speech pathologists for voice training is most effective.

generally maximal at 2 yr after initiation of hormones (82, 83, 84). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in MTF transsexual persons has been studied (97), precise information about other changes induced by sex hormones is lacking. There is a great deal of variability between individuals, as evidenced during pubertal development.

3.4 Values and Preferences

Transsexual persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.* breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone-induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse outcome prevention and long-term care

Cross-sex hormone therapy confers the same risks associated with sex hormone replacement therapy in biological males and females. The risk of cross-sex hormone therapy arises from and is worsened by inadvertent or intentional use of supraphysiological doses of sex hormones or inadequate doses of sex hormones to maintain normal physiology (81, 89).

4.1 Recommendation

We suggest regular clinical and laboratory monitoring every 3 months during the first year and then once or twice yearly. (2 ⊕⊕○○)

4.1 Evidence

Pretreatment screening and appropriate regular medical monitoring is recommended for both FTM and MTF transsexual persons during the endocrine transition and periodically thereafter (13, 97). Monitoring of weight and blood pressure, directed physical exams, routine health questions focused on risk factors and medications, complete blood counts, renal and liver function, lipid and glucose metabolism should be carried out.

FTM transsexual persons

A standard monitoring plan for individuals on testosterone therapy is found in Table 15. Key issues include maintaining testosterone levels in the physiological normal male range and avoidance of adverse events resulting from chronic testosterone therapy, particularly erythrocytosis, liver dysfunction, hypertension, excessive weight gain, salt retention, lipid changes, excessive or cystic acne, and adverse psychological changes (85).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with the use parenteral or transdermal testosterone (98, 99). Still, periodic monitoring is recommended given that up to 15% of FTM persons treated with testosterone have transient elevations in liver enzymes (93).

MTF transsexual persons

A standard monitoring plan for individuals on estrogens, gonadotropin suppression, or antiandrogens is found in Table 16. Key issues include avoiding supraphysiological doses or blood levels of estrogen, which may lead to increased risk for thromboembolic disease, liver dysfunction, and development of hypertension.

4.2 Recommendation

We suggest monitoring prolactin levels in MTF transsexual persons treated with estrogens. (2 ⊕⊕○○)

4.2 Evidence

Estrogen therapy can increase the growth of pituitary lactotroph cells. There have been several reports of prolactino-

mas occurring after long-term estrogen therapy (100–102). Up to 20% of transsexual women treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (103). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy (104).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Prolactin levels should be obtained at baseline and then at least annually during the transition period and biannually thereafter. Given that prolactinomas have been reported only in a few case reports and were not reported in large cohorts of estrogen-treated transsexual persons, the risk of prolactinoma is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in MTF transsexual persons, radiological examination of the pituitary may be carried out in those whose prolactin levels persistently increase despite stable or reduced estrogen levels.

Because transsexual persons are diagnosed and followed throughout sex reassignment by an MHP, it is likely that some will receive psychotropic medications that can increase prolactin levels.

4.3 Recommendation

We suggest that transsexual persons treated with hormones be evaluated for cardiovascular risk factors. (2 ⊕⊕○○)

4.3 Evidence

FTM transsexual persons

Testosterone administration to FTM transsexual persons will result in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride values (21, 105–107). Studies of the effect of testosterone on insulin sensitivity have mixed results (106, 108). A recent randomized, open-label uncontrolled safety study of FTM transsexual persons treated with testosterone undecanoate demonstrated no insulin resistance after 1 yr (109). Numerous studies have demonstrated

TABLE 15. Monitoring of MTF transsexual persons on cross-hormone therapy

1. Evaluate patient every 2–3 months in the first year and then 1–2 times per year afterward to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 months.
 - a. Serum testosterone levels should be <55 ng/dl.
 - b. Serum estradiol should not exceed the peak physiological range for young healthy females, with ideal levels <200 pg/ml.
 - c. Doses of estrogen should be adjusted according to the serum levels of estradiol.
3. For individuals on spironolactone, serum electrolytes (particularly potassium) should be monitored every 2–3 months initially in the first year.
4. Routine cancer screening is recommended in nontranssexual individuals (breasts, colon, prostate).
5. Consider BMD testing at baseline if risk factors for osteoporotic fracture are present (e.g. previous fracture, family history, glucocorticoid use, prolonged hypogonadism). In individuals at low risk, screening for osteoporosis should be conducted at age 60 and in those who are not compliant with hormone therapy.

TABLE 16. Monitoring of FTM transsexual persons on cross-hormone therapy

1. Evaluate patient every 2–3 months in the first year and then 1–2 times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 2–3 months until levels are in the normal physiological male range:^a
 - a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. If the level is >700 ng/dl or <350 ng/dl, adjust dose accordingly.
 - b. For parenteral testosterone undecanoate, testosterone should be measured just before the next injection.
 - c. For transdermal testosterone, the testosterone level can be measured at any time after 1 wk.
 - d. For oral testosterone undecanoate, the testosterone level should be measured 3–5 h after ingestion.
 - e. Note: During the first 3–9 months of testosterone treatment, total testosterone levels may be high, although free testosterone levels are normal, due to high SHBG levels in some biological women.
3. Measure estradiol levels during the first 6 months of testosterone treatment or until there has been no uterine bleeding for 6 months. Estradiol levels should be <50 pg/ml.
4. Measure complete blood count and liver function tests at baseline and every 3 months for the first year and then 1–2 times a year. Monitor weight, blood pressure, lipids, fasting blood sugar (if family history of diabetes), and hemoglobin A1c (if diabetic) at regular visits.
5. Consider BMD testing at baseline if risk factors for osteoporotic fracture are present (e.g. previous fracture, family history, glucocorticoid use, prolonged hypogonadism). In individuals at low risk, screening for osteoporosis should be conducted at age 60 and in those who are not compliant with hormone therapy.
6. If cervical tissue is present, an annual pap smear is recommended by the American College of Obstetricians and Gynecologists.
7. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

^a Adapted from Refs. 83 and 85.

effects of cross-sex hormone treatment on the cardiovascular system (107, 110–112). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (93). Likewise, a meta-analysis of 19 randomized trials examining testosterone replacement in men showed no increased incidence of cardiovascular events (113). A systematic review of the literature found that data were insufficient, due to very low quality evidence, to allow meaningful assessment of important patient outcomes such as death, stroke, myocardial infarction, or venous thromboembolism in FTM transsexual persons (21). Future research is needed to ascertain harms of hormonal therapies (21). Cardiovascular risk factors should be managed as they emerge according to established guidelines (114).

MTF transsexual persons

A prospective study of MTF subjects found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (106). However, these favorable lipid changes were attenuated by increased weight, blood pressure, and markers of insulin resistance. The largest cohort of MTF subjects (with a mean age of 41 yr) followed for a mean of 10 yr showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (93). Thus, there is limited evidence to determine whether estrogen is protective or detrimental in MTF transsexual persons (21). With aging there is usually an increase of body weight, and therefore, as with nontranssexual individuals, glucose and lipid metabolism and blood pressure should be monitored regularly and managed according to established guidelines (114).

4.4 Recommendation

We suggest that BMD measurements be obtained if risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (2 ⊕⊕⊕○)

4.4 Evidence

FTM transsexual persons

Adequate dosing of testosterone is important to maintain bone mass in FTM transsexual persons (115, 116). In one study (116), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol both systemically and locally in the bone.

MTF transsexual persons

Studies in aging genetic males suggest that serum estradiol more positively correlates with BMD than does testosterone (117–119) and is more important for peak bone mass (120). Estrogen preserves BMD in MTF transsexuals who continue on estrogen and antiandrogen therapies (116, 121, 122).

Fracture data in transsexual men and women are not available. Transsexual persons who have undergone gonadectomy may not continue consistent cross-sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss.

4.5–4.6 Recommendations

4.5 We suggest that MTF transsexual persons who have no known increased risk of breast cancer follow breast

screening guidelines recommended for biological women. (2 ⊕⊕⊕⊕)

4.6 We suggest that MTF transsexual persons treated with estrogens follow screening guidelines for prostatic disease and prostate cancer recommended for biological men. (2 ⊕⊕⊕⊕)

4.5–4.6 Evidence

Breast cancer is a concern in transsexual women. A few cases of breast cancer in MTF transsexual persons have been reported in the literature (123–125). In the Dutch cohort of 1800 transsexual women followed for a mean of 15 yr (range, 1 to 30 yr), only one case of breast cancer was found. The Women's Health Initiative study reported that women taking conjugated equine estrogen without progesterone for 7 yr did not have an increased risk of breast cancer as compared with women taking placebo (126). Women with primary hypogonadism (XO) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (127, 128). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short-term (<20–30 yr). Long-term studies are required to determine the actual risk and the role of screening mammograms. Regular exams and gynecological advice should determine monitoring for breast cancer.

Prostate cancer is very rare, especially with androgen deprivation therapy, before the age of 40 (129). Childhood or pubertal castration results in regression of the prostate, and adult castration reverses benign prostate hypertrophy (130). Although van Kesteren (131) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostate of MTF transsexual persons, cases of benign prostate hypertrophy have been reported in MTF transsexual persons treated with estrogens for 20–25 yr (132, 133). Three cases of prostate carcinoma have been reported in MTF transsexual persons (134–136). However, these individuals initiated cross-hormone therapy after age 50, and whether these cancers were present before the initiation of therapy is unknown.

MTF transsexual persons may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for MTF transsexual persons who transitioned after age 20 to have annual screening digital rectal exams after age 50 and PSA tests consistent with the U.S. Preventive Services Task Force Guidelines (137).

4.7 Recommendation

We suggest that FTM transsexual persons evaluate the risks and benefits of including a total hysterectomy

and oophorectomy as part of sex reassignment surgery. (2 ⊕⊕⊕⊕)

4.7 Evidence

Although aromatization of testosterone to estradiol in FTM transsexual persons has been suggested as a risk factor for endometrial cancer (138), no cases have been reported. When FTM transsexual persons undergo hysterectomy, the uterus is small and there is endometrial atrophy (139, 140). The androgen receptor has been reported to increase in the ovaries after long-term administration of testosterone, which may be an indication of increased risk of ovarian cancer (141). Cases of ovarian cancer have been reported (142, 143). The relative safety of laparoscopic total hysterectomy argues for preventing the risks of reproductive tract cancers and other diseases through surgery (144).

4.7 Values and Preferences

Given the discomfort that FTM transsexual persons experience accessing gynecological care, our recommendation for total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

4.7 Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecological care required after transition. In addition, approval of birth certificate change of sex for FTM transsexual persons may be dependent upon having a complete hysterectomy; each patient should be assisted in researching and counseled concerning such nonmedical administrative criteria.

5.0 Surgery for sex reassignment

For many transsexual adults, genital sex reassignment surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. Although surgery on several different body structures is considered during sex reassignment, the most important issue is the genital surgery and removal of the gonads. The surgical techniques have improved markedly during the past 10 yr. Cosmetic genital surgery with preservation of neurological sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (22). In addition, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender identity treatment that

TABLE 17. Sex reassignment surgery eligibility and readiness criteria

Individuals treated with cross-sex hormones are considered eligible for sex reassignment surgery if they:
1. Are of the legal age of majority in their nation.
2. Have used cross-sex hormones continuously and responsibly during 12 months (if they have no medical contraindication).
3. Had a successful continuous full-time RLE during 12 months.
4. Have (if required by the MHP) regularly participated in psychotherapy throughout the RLE at a frequency determined jointly by the patient and the MHP.
5. Have shown demonstrable knowledge of all practical aspects of surgery (e.g. cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation, etc.).
Individuals treated with cross-sex hormones should fulfill the following readiness criteria prior to sex reassignment surgery:
1. Demonstrable progress in consolidating one's gender identity.
2. Demonstrable progress in dealing with work, family, and interpersonal issues, resulting in a significantly better state of mental health.

includes hormones and surgery (24). The person must be both eligible and ready for such a procedure (Table 17).

Sex reassignment surgeries available to the MTF transsexual persons consist of gonadectomy, penectomy, and creation of a vagina (145, 146). The skin of the penis is often inverted to form the wall of the vagina. The scrotum becomes the labia majora. Cosmetic surgery is used to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Most recently, plastic surgeons have developed techniques to fashion labia minora. Endocrinologists should encourage the transsexual person to use their tampon dilators to maintain the depth and width of the vagina throughout the postoperative period until the neovagina is being used frequently in intercourse. Genital sexual responsivity and other aspects of sexual function should be preserved after genital sex reassignment surgery (147).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. When possible, less surgery is desirable. For instance, voice therapy by a speech language pathologist is preferred to current surgical methods designed to change the pitch of the voice (148).

Breast size in genetic females exhibits a very broad spectrum. For the transsexual person to make the best-informed decision, breast augmentation surgery should be delayed until at least 2 yr of estrogen therapy has been completed, given that the breasts continue to grow during that time with estrogen stimulation (90, 97).

Another major effort is the removal of facial and masculine-appearing body hair using either electrolysis or laser treatments. Other feminizing surgery, such as that to feminize the face, is now becoming more popular (149–151).

Sex reassignment surgeries available to the FTM transsexual persons have been less satisfactory. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (152, 153). Neopenile erection can be achieved only if some mechanical device is imbedded in the penis, e.g. a rod or some inflatable apparatus (154). Many choose a metoidioplasty that exteriorizes or brings forward the clitoris and allows for voiding while standing. The scrotum is created from the labia majora with a good cosmetic effect, and testicular prostheses can be implanted. These procedures, as well as oophorectomy, vaginectomy, and complete hysterectomy, are undertaken after a few years of androgen therapy and can be safely performed vaginally with laparoscopy.

The ancillary surgery for the FTM transition that is extremely important is the mastectomy. Breast size only partially regresses with androgen therapy. In adults, discussion about mastectomy usually takes place after androgen therapy is begun. Because some FTM transsexual adolescents present after significant breast development has occurred, mastectomy may be considered before age 18.

5.1–5.3 Recommendations

5.1 We recommend that transsexual persons consider genital sex reassignment surgery only after both the physician responsible for endocrine transition therapy and the MHP find surgery advisable. (1 ⊕○○○)

5.2 We recommend that genital sex reassignment surgery be recommended only after completion of at least 1 yr of consistent and compliant hormone treatment. (1 ⊕○○○)

5.3 We recommend that the physician responsible for endocrine treatment medically clear transsexual individuals for sex reassignment surgery and collaborate with the surgeon regarding hormone use during and after surgery. (1 ⊕○○○)

5.1–5.3 Evidence

When a transsexual individual decides to have sex reassignment surgery, both the endocrinologist and the MHP must certify that he or she satisfies the eligibility and readiness criteria of the SOC (28) (Table 17).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or after surgery (21). For this reason, the surgeon and the endocrinologist should collaborate in making a decision about the use of hormones during the month before surgery.

Although one study suggests that preoperative factors such as compliance are less important for patient satisfaction than are the physical postoperative results (39), other studies and clinical experience dictate that individuals who do not follow medical instructions and work with their physicians toward a common goal do not achieve treatment goals (155) and experience higher rates of postoperative infections and other complications (156, 157). It is also important that the person requesting surgery feel comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (78).

Transsexual individuals should be monitored by an endocrinologist after surgery. Those who undergo gonadectomy will require hormone replacement therapy or surveillance or both to prevent adverse effects of chronic hormone deficiency.

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References

1. Bullough VL 1975 Transsexualism in history. *Arch Sex Behav* 4:561–571
2. Meyerowitz J 2002 How sex changed: a history of transsexuality in the United States. Cambridge, MA: Harvard University Press
3. American Psychiatric Association 2000 Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Publishing, Inc.
4. Ruble DN, Martin CL, Berenbaum SA 2006 Gender development. In: Damon W, Lerner RM, Eisenberg N, eds. Handbook of child psychology, 6th ed. Vol. 3. New York: John Wiley & Sons; 858–932
5. Zucker KJ 2004 Gender identity development and issues. *Child Adolesc Psychiatr Clin N Am* 13:551–568, vii
6. Coolidge FL, Thede LL, Young SE 2002 The heritability of gender identity disorder in a child and adolescent twin sample. *Behav Genet* 32:251–257
7. Knafo A, Iervolino AC, Plomin R 2005 Masculine girls and feminine boys: genetic and environmental contributions to atypical gender development in early childhood. *J Pers Soc Psychol* 88:400–412
8. Gooren L 2006 The biology of human psychosexual differentiation. *Horm Behav* 50:589–601
9. Meyer-Bahlburg HF 2005 Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. *Arch Sex Behav* 34:423–438
10. Reiner WG 2005 Gender identity and sex-of-rearing in children with disorders of sexual differentiation. *J Pediatr Endocrinol Metab* 18:549–553
11. Dessens AB, Slijper FM, Drop SL 2005 Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Arch Sex Behav* 34:389–397
12. Meyer-Bahlburg HF, Dolezal C, Baker SW, Carlson AD, Obeid JS, New MI 2004 Prenatal androgenization affects gender-related behavior but not gender identity in 5–12-year-old girls with congenital adrenal hyperplasia. *Arch Sex Behav* 33:97–104
13. Meyer-Bahlburg HF, Dolezal C, Baker SW, Ehrhardt AA, New MI 2006 Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. *Arch Sex Behav* 35: 667–684
14. Bocklandt S, Vilain E 2007 Sex differences in brain and behavior: hormones versus genes. *Adv Genet* 59:245–266
15. Blanchard R 1997 Birth order and sibling sex ratio in homosexual versus heterosexual males and females. *Annu Rev Sex Res* 8:27–67
16. Blanchard R 2001 Fraternal birth order and the maternal immune hypothesis of male homosexuality. *Horm Behav* 40:105–114
17. Whitehead NE 2007 An antibody antibody? Re-examination of the maternal immune hypothesis. *J Biosoc Sci* 39:905–921
18. Gooren L 1990 The endocrinology of transsexualism: a review and commentary. *Psychoneuroendocrinology* 15:3–14
19. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer TT, Varonen H, Vist GE, Williams Jr JW, Zaza S 2004 Grading quality of evidence and strength of recommendations. *BMJ* 328:1490

20. Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM 2008 A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab* 93:666–673
21. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM 16 May 2009 Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 10.1111/j.1365–2265.2009.03632.x
22. Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM 16 May 2009 Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)* 10.1111/j.1365–2265.2009.03625.x
23. Cohen-Kettenis PT, Owen A, Kaijser VG, Bradley SJ, Zucker KJ 2003 Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: a cross-national, cross-clinic comparative analysis. *J Abnorm Child Psychol* 31:41–53
24. Cole CM, O'Boyle M, Emory LE, Meyer 3rd WJ 1997 Comorbidity of gender dysphoria and other major psychiatric diagnoses. *Arch Sex Behav* 26:13–26
25. Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A 2005 Psychiatric comorbidity in gender identity disorder. *J Psychosom Res* 58:259–261
26. Kersting A, Reutemann M, Gast U, Ohrmann P, Suslow T, Michael N, Arolt V 2003 Dissociative disorders and traumatic childhood experiences in transsexuals. *J Nerv Ment Dis* 191:182–189
27. Wallien MS, Swaab H, Cohen-Kettenis PT 2007 Psychiatric comorbidity among children with gender identity disorder. *J Am Acad Child Adolesc Psychiatry* 46:1307–1314
28. Meyer 3rd WJ, Bockting W, Cohen-Kettenis P, Coleman E, DiCeglie D, Devor H, Gooren L, Hage JJ, Kirk S, Kuiper B, Laub D, Lawrence A, Menard Y, Monstrey S, Patton J, Schaefer L, Webb A, Wheeler CC 2001 Harry Benjamin International Gender Dysphoria Association's The Standards of Care for Gender Identity Disorders, 6th version. *Int J Transgenderism*, vol. 5, no. 1. Available at: http://www.symposion.com/ijt/soc_2001/index.htm
29. 1992 The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization
30. Kuiper AJ, Cohen-Kettenis PT 1998 Gender role reversal among postoperative transsexuals. *Int J Transgenderism*, vol. 2, no. 3. Available at: <http://www.symposion.com/ijt/ijt0502.htm>
31. Landén M, Wälinder J, Hambert G, Lundström B 1998 Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand* 97: 284–289
32. Olsson SE, Möller A 2006 Regret after sex reassignment surgery in a male-to-female transsexual: a long-term follow-up. *Arch Sex Behav* 35:501–506
33. Pfäfflin F, Junge A 1992 Geschlechtsumwandlung: Abhandlungen zur Transsexualität [Sex change: treatises on transsexualism]. Stuttgart, Germany: Schattauer
34. Cohen-Kettenis PT, Pfäfflin F 2003 Transgenderism and intersexuality in childhood and adolescence: making choices. Thousand Oaks, CA: Sage Publications
35. Di Ceglie D, Freedman D, McPherson S, Richardson P 2002 Children and adolescents referred to a specialist gender identity development service: clinical features and demographic characteristics. *Int J Transgenderism*, vol. 6, no. 1. Available at: http://www.symposion.com/ijt/ijtvo06no01_01.htm
36. Cohen-Kettenis PT, van Goozen SH 1997 Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry* 36:263–271
37. Smith YL, van Goozen SH, Cohen-Kettenis PT 2001 Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry* 40:472–481
38. Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT 2005 Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med* 35:89–99
39. Lawrence AA 2003 Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav* 32:299–315
40. Seikowski K 2007 Psychotherapy and transsexualism. *Andrologia* 39:248–252
41. Coleman E, Cesnik J 1990 Skoptic syndrome: the treatment of an obsessional gender dysphoria with lithium carbonate and psychotherapy. *Am J Psychother* 44:204–217
42. Cohen-Kettenis PT 2001 Gender identity disorder in DSM? *J Am Acad Child Adolesc Psychiatry* 40:391
43. Drummond KD, Bradley SJ, Peterson-Badali M, Zucker KJ 2008 A follow-up study of girls with gender identity disorder. *Dev Psychol* 44:34–45
44. Wallien MS, Cohen-Kettenis PT 2008 Psychosexual outcome of gender-dysphoric children. *J Am Acad Child Adolesc Psychiatry* 47:1413–1423
45. Zucker KJ, Bradley SJ 1995 Gender identity disorder and psychosexual problems in children and adolescents. New York: Guilford Press
46. Büchter D, Behre HM, Kliesch S, Nieschlag E 1998 Pulsatile GnRH or human chorionic gonadotropin/human menopausal gonadotropin as effective treatment for men with hypogonadotropic hypogonadism: a review of 42 cases. *Eur J Endocrinol* 139:298–303
47. Liu PY, Turner L, Rushford D, McDonald J, Baker HW, Conway AJ, Handelsman DJ 1999 Efficacy and safety of recombinant human follicle stimulating hormone (Gonal-F) with urinary human chorionic gonadotrophin for induction of spermatogenesis and fertility in gonadotrophin-deficient men. *Hum Reprod* 14: 1540–1545
48. De Sutter P 2001 Gender reassignment and assisted reproduction: present and future reproductive options for transsexual people. *Hum Reprod* 16:612–614
49. De Sutter P 2007 Reproduction and fertility issues for transpeople. In: Ettner R, Monstrey S, Eyler AE, eds. *Principles of transgender medicine and surgery*. New York: Haworth Press; 209–221
50. Seli E, Tangir J 2005 Fertility preservation options for female patients with malignancies. *Curr Opin Obstet Gynecol* 17:299–308
51. Lübbert H, Leo-Rossberg I, Hammerstein J 1992 Effects of ethinyl estradiol on semen quality and various hormonal parameters in a eugonadal male. *Fertil Steril* 58:603–608
52. Schulze C 1988 Response of the human testis to long-term estrogen treatment: morphology of Sertoli cells, Leydig cells and spermatogonial stem cells. *Cell Tissue Res* 251:31–43
53. Thiagaraj D, Gunasegaram R, Loganath A, Peh KL, Kottegoda SR, Ratnam SS 1987 Histopathology of the testes from male transsexuals on oestrogen therapy. *Ann Acad Med Singapore* 16:347–348
54. Baba T, Endo T, Honnma H, Kitajima Y, Hayashi T, Ikeda H, Masumori N, Kamiya H, Moriwaka O, Saito T 2007 Association between polycystic ovary syndrome and female-to-male transsexuality. *Hum Reprod* 22:1011–1016
55. Spinder T, Spijkstra JJ, van den Tweel JG, Burger CW, van Kessel H, Hompes PG, Gooren LJ 1989 The effects of long-term testosterone administration on pulsatile luteinizing hormone secretion and on ovarian histology in eugonadal female to male transsexual subjects. *J Clin Endocrinol Metab* 69:151–157
56. Trebay G 2008 He's pregnant, you're speechless. *New York Times*, June 28, 2008; 18
57. De Sutter P 2003 Donor inseminations in partners of female-to-male transsexuals: should the question be asked? *Reprod Biomed Online* 6:382; author reply 282–283
58. Boyar RM, Wu RH, Roffwarg H, Kapen S, Weitzman ED, Hellman L, Finkelstein JW 1976 Human puberty: 24-hour estradiol in pubertal girls. *J Clin Endocrinol Metab* 43:1418–1421

59. Wennink JM, Delemarre-van de Waal HA, Schoemaker R, Schoemaker H, Schoemaker J 1989 Luteinizing hormone and follicle stimulating hormone secretion patterns in boys throughout puberty measured using highly sensitive immunoradiometric assays. *Clin Endocrinol (Oxf)* 31:551–564
60. Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJ 2008 The treatment of adolescent transsexuals: changing insights. *J Sex Med* 5:1892–1897
61. Delemarre-Van de Waal HA, Cohen-Kettenis PT 2006 Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol* 155(Suppl 1):S131–S137
62. Tanner JM 1962 Growth at adolescence. 2nd ed. Oxford, UK: Blackwell Scientific Publications
63. Wennink JM, Delemarre-van de Waal HA, Schoemaker R, Schoemaker H, Schoemaker J 1990 Luteinizing hormone and follicle stimulating hormone secretion patterns in girls throughout puberty measured using highly sensitive immunoradiometric assays. *Clin Endocrinol (Oxf)* 33:333–344
64. Roth C 2002 Therapeutic potential of GnRH antagonists in the treatment of precocious puberty. *Expert Opin Investig Drugs* 11:1253–1259
65. Tuvemo T 2006 Treatment of central precocious puberty. *Expert Opin Investig Drugs* 15:495–505
66. Manasco PK, Pescovitz OH, Feuillan PP, Hench KD, Barnes KM, Jones J, Hill SC, Loriaux DL, Cutler Jr GB 1988 Resumption of puberty after long term luteinizing hormone-releasing hormone agonist treatment of central precocious puberty. *J Clin Endocrinol Metab* 67:368–372
67. Mittan D, Lee S, Miller E, Perez RC, Basler JW, Bruder JM 2002 Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. *J Clin Endocrinol Metab* 87:3656–3661
68. Neely EK, Bachrach LK, Hintz RL, Habiby RL, Slemenda CW, Feezle L, Pescovitz OH 1995 Bone mineral density during treatment of central precocious puberty. *J Pediatr* 127:819–822
69. Raudrant D, Rabe T 2003 Progestogens with antiandrogenic properties. *Drugs* 63:463–492
70. Jain J, Dutton C, Nicosia A, Wajszczuk C, Bode FR, Mishell Jr DR 2004 Pharmacokinetics, ovulation suppression and return to ovulation following a lower dose subcutaneous formulation of Depo-Provera. *Contraception* 70:11–18
71. Mieszczyk J, Eugster EA 2007 Treatment of precocious puberty in McCune-Albright syndrome. *Pediatr Endocrinol Rev* 4(Suppl 4):419–422
72. Richman RA, Underwood LE, French FS, Van Wyk JJ 1971 Adverse effects of large doses of medroxyprogesterone (MPA) in idiopathic isosexual precocity. *J Pediatr* 79:963–971
73. Albanese A, Kewley GD, Long A, Pearl KN, Robins DG, Stanhope R 1994 Oral treatment for constitutional delay of growth and puberty in boys: a randomised trial of an anabolic steroid or testosterone undecanoate. *Arch Dis Child* 71:315–317
74. Nilsson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenäs L, Häger A, Ivarsson SA, Karlberg J, Kriström B, Marcus C, Moell C, Ritzen M, Tuvemo T, Wattsgård C, Westgren U, Westphal O, Aman J 1996 Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. *J Clin Endocrinol Metab* 81:635–640
75. Schroor EJ, van Weissenbruch MM, Knibbe P, Delemarre-van de Waal HA 1995 The effect of prolonged administration of an anabolic steroid (oxandrolone) on growth in boys with constitutionally delayed growth and puberty. *Eur J Pediatr* 154:953–957
76. Ball GD, Huang TT, Gower BA, Cruz ML, Shaibi GQ, Weigensberg MJ, Goran MI 2006 Longitudinal changes in insulin sensitivity, insulin secretion, and β -cell function during puberty. *J Pediatr* 148:16–22
77. Reinehr T, Kiess W, Andler W 2005 Insulin sensitivity indices of glucose and free fatty acid metabolism in obese children and adolescents in relation to serum lipids. *Metabolism* 54:397–402
78. Monstrey S, De Cuyper G, Ettner R 2007 Surgery: general principles. In: Ettner SR, Monstrey S, Eyler AE, eds. *Principles of transgender medicine and surgery*. New York: Haworth Press; 89–104
79. Monstrey S, Hoebeke P, Dhont M, De Cuyper G, Rubens R, Moerman M, Hamdi M, Van Landuyt K, Blondeel P 2001 Surgical therapy in transsexual patients: a multi-disciplinary approach. *Acta Chir Belg* 101:200–209
80. Gooren L 2005 Hormone treatment of the adult transsexual patient. *Horm Res* 64(Suppl 2):31–36
81. Gooren LJ, Giltay EJ 2008 Review of studies of androgen treatment of female-to-male transsexuals: effects and risks of administration of androgens to females. *J Sex Med* 5:765–776
82. Levy A, Crown A, Reid R 2003 Endocrine intervention for transsexuals. *Clin Endocrinol (Oxf)* 59:409–418
83. Moore E, Wisniewski A, Dobs A 2003 Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. *J Clin Endocrinol Metab* 88:3467–3473
84. Tangpricha V, Ducharme SH, Barber TW, Chipkin SR 2003 Endocrinologic treatment of gender identity disorders. *Endocr Pract* 9:12–21
85. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM 2006 Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 91:1995–2010
86. Bolaña ER, Uraga MV, Haddad RM, Tracz MJ, Sideras K, Kennedy CC, Caples SM, Erwin PJ, Montori VM 2007 Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 82:20–28
87. Dickersin K, Munro MG, Clark M, Langenberg P, Scherer R, Frick K, Zhu Q, Hallock L, Nichols J, Yalcinkaya TM 2007 Hysterec-tomy compared with endometrial ablation for dysfunctional uterine bleeding: a randomized controlled trial. *Obstet Gynecol* 110:1279–1289
88. Prasad P, Powell MC 2008 Prospective observational study of Thermablate Endometrial Ablation System as an outpatient procedure. *J Minim Invasive Gynecol* 15:476–479
89. Gooren LJ, Giltay EJ, Bunck MC 2008 Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 93:19–25
90. Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann MW, Mueller A 2005 Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes* 113:586–592
91. Levy J, Burshell A, Marbach M, Afflalo L, Glick SM 1980 Interaction of spironolactone with oestradiol receptors in cytosol. *J Endocrinol* 84:371–379
92. Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, Gooren LJ, Rosing J 2003 Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. *J Clin Endocrinol Metab* 88:5723–5729
93. van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ 1997 Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)* 47:337–342
94. Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB 5 February 2009 Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. *Fertil Steril* 10.1016/j.fertnstert.2008.12.017
95. Righini M, Perrier A, De Moerloose P, Bounameaux H 2008 D-dimer for venous thromboembolism diagnosis: 20 years later. *J Thromb Haemost* 6:1059–1071
96. Lapauw B, Taes Y, Simoens S, Van Caenegem E, Weyers S, Goemaere S, Toye K, Kaufman JM, T'Sjoen GG 2008 Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. *Bone* 43:1016–1021

97. Meyer 3rd WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA 1986 Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav* 15:121–138
98. Bird D, Vowles K, Anthony PP 1979 Spontaneous rupture of a liver cell adenoma after long term methyltestosterone: report of a case successfully treated by emergency right hepatic lobectomy. *Br J Surg* 66:212–213
99. Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM 1977 Liver damage from long-term methyltestosterone. *Lancet* 2:262–263
100. Gooren LJ, Assies J, Asscheman H, de Slegte R, van Kessel H 1988 Estrogen-induced prolactinoma in a man. *J Clin Endocrinol Metab* 66:444–446
101. Kovacs K, Stefaneanu L, Ezzat S, Smyth HS 1994 Prolactin-producing pituitary adenoma in a male-to-female transsexual patient with protracted estrogen administration: a morphologic study. *Arch Pathol Lab Med* 118:562–565
102. Serri O, Noiseux D, Robert F, Hardy J 1996 Lactotroph hyperplasia in an estrogen treated male-to-female transsexual patient. *J Clin Endocrinol Metab* 81:3177–3179
103. Asscheman H, Gooren LJ, Assies J, Smits JP, de Slegte R 1988 Prolactin levels and pituitary enlargement in hormone-treated male-to-female transsexuals. *Clin Endocrinol (Oxf)* 28:583–588
104. Gooren LJ, Harmsen-Louman W, van Kessel H 1985 Follow-up of prolactin levels in long-term oestrogen-treated male-to-female transsexuals with regard to prolactinoma induction. *Clin Endocrinol (Oxf)* 22:201–207
105. Berra M, Armillotta F, D'Emidio L, Costantino A, Martorana G, Pelusi G, Meriggiola MC 2006 Testosterone decreases adiponectin levels in female to male transsexuals. *Asian J Androl* 8:725–729
106. Elbers JM, Giltay EJ, Teerlink T, Scheffer PG, Asscheman H, Seidell JC, Gooren LJ 2003 Effects of sex steroids on components of the insulin resistance syndrome in transsexual subjects. *Clin Endocrinol (Oxf)* 58:562–571
107. Giltay EJ, Lambert J, Gooren LJ, Elbers JM, Steyn M, Stehouwer CD 1999 Sex steroids, insulin, and arterial stiffness in women and men. *Hypertension* 34:590–597
108. Polderman KH, Gooren LJ, Asscheman H, Bakker A, Heine RJ 1994 Induction of insulin resistance by androgens and estrogens. *J Clin Endocrinol Metab* 79:265–271
109. Meriggiola MC, Armillotta F, Costantino A, Altieri P, Saad F, Kalhorn T, Perrone AM, Ghi T, Pelusi C, Pelusi G 2008 Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. *J Sex Med* 5:2442–2453
110. Giltay EJ, Hoogeveen EK, Elbers JM, Gooren LJ, Asscheman H, Stehouwer CD 1998 Effects of sex steroids on plasma total homocysteine levels: a study in transsexual males and females. *J Clin Endocrinol Metab* 83:550–553
111. Giltay EJ, Toorians AW, Sarabdjitsingh AR, de Vries NA, Gooren LJ 2004 Established risk factors for coronary heart disease are unrelated to androgen-induced baldness in female-to-male transsexuals. *J Endocrinol* 180:107–112
112. Giltay EJ, Verhoef P, Gooren LJ, Geleijnse JM, Schouten EG, Stehouwer CD 2003 Oral and transdermal estrogens both lower plasma total homocysteine in male-to-female transsexuals. *Atherosclerosis* 168:139–146
113. Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL, Bhasin S 2005 Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci* 60:1451–1457
114. NCEP 2002 Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 106:3143–3421
115. Turner A, Chen TC, Barber TW, Malabanan AO, Holick MF, Tangpricha V 2004 Testosterone increases bone mineral density in female-to-male transsexuals: a case series of 15 subjects. *Clin Endocrinol (Oxf)* 61:560–566
116. van Kesteren P, Lips P, Gooren LJ, Asscheman H, Megens J 1998 Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. *Clin Endocrinol (Oxf)* 48:347–354
117. Amin S, Zhang Y, Sawin CT, Evans SR, Hannan MT, Kiel DP, Wilson PW, Felson DT 2000 Association of hypogonadism and estradiol levels with bone mineral density in elderly men from the Framingham study. *Ann Intern Med* 133:951–963
118. Gennari L, Khosla S, Bilezikian JP 2008 Estrogen and fracture risk in men. *J Bone Miner Res* 23:1548–1551
119. Gennari L, Khosla S, Bilezikian JP 2008 Estrogen effects on bone in the male skeleton. In: Bilezikian JP, Martin TJ, Raisz LG, eds. *Principles of bone biology*. 3rd ed. San Diego: Academic Press; 1801–1818
120. Khosla S, Melton 3rd LJ, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL 1998 Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. *J Clin Endocrinol Metab* 83:2266–2274
121. Mueller A, Ditttrich R, Binder H, Kuehnel W, Maltaris T, Hoffmann I, Beckmann MW 2005 High dose estrogen treatment increases bone mineral density in male-to-female transsexuals receiving gonadotropin-releasing hormone agonist in the absence of testosterone. *Eur J Endocrinol* 153:107–113
122. Ruetsche AG, Kneubuehl R, Birkhaeuser MH, Lippuner K 2005 Cortical and trabecular bone mineral density in transsexuals after long-term cross-sex hormonal treatment: a cross-sectional study. *Osteoporos Int* 16:791–798
123. Ganly I, Taylor EW 1995 Breast cancer in a trans-sexual man receiving hormone replacement therapy. *Br J Surg* 82:341
124. Pritchard TJ, Pankowsky DA, Crowe JP, Abdul-Karim FW 1988 Breast cancer in a male-to-female transsexual. A case report. *JAMA* 259:2278–2280
125. Symmers WS 1968 Carcinoma of breast in trans-sexual individuals after surgical and hormonal interference with the primary and secondary sex characteristics. *Br Med J* 2:83–85
126. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, Bonds D, Brunner R, Brzyski R, Caan B, Chlebowski R, Curb D, Gass M, Hays J, Heiss G, Hendrix S, Howard BV, Hsia J, Hubbell A, Jackson R, Johnson KC, Judd H, Kotchen JM, Kuller L, LaCroix AZ, Lane D, Langer RD, Lasser N, Lewis CE, Manson J, Margolis K, Ockene J, O'Sullivan MJ, Phillips L, Prentice RL, Ritenbaugh C, Robbins J, Rossouw JE, Sarto G, Stefanick ML, Van Horn L, Wactawski-Wende J, Wallace R, Wassertheil-Smolter S 2004 Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 291:1701–1712
127. Bösze P, Tóth A, Török M 2006 Hormone replacement and the risk of breast cancer in Turner's syndrome. *N Engl J Med* 355:2599–2600
128. Schoemaker MJ, Swerdlow AJ, Higgins CD, Wright AF, Jacobs PA 2008 Cancer incidence in women with Turner syndrome in Great Britain: a national cohort study. *Lancet Oncol* 9:239–246
129. Smith RA, Cokkinides V, Eyre HJ 2006 American Cancer Society guidelines for the early detection of cancer, 2006. *CA Cancer J Clin* 56:11–25; quiz 49–50
130. Wilson JD, Roehrborn C 1999 Long-term consequences of castration in men: lessons from the Skoptzy and the eunuchs of the Chinese and Ottoman courts. *J Clin Endocrinol Metab* 84:4324–4331
131. van Kesteren P, Meinhardt W, van der Valk P, Geldof A, Megens J, Gooren L 1996 Effects of estrogens only on the prostates of aging men. *J Urol* 156:1349–1353
132. Brown JA, Wilson TM 1997 Benign prostatic hyperplasia requiring transurethral resection of the prostate in a 60-year-old male-to-female transsexual. *Br J Urol* 80:956–957
133. Casella R, Bubendorf L, Schaefer DJ, Bachmann A, Gasser TC,

- Sulser T 2005 Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int* 75:288–290
134. Dorff TB, Shazer RL, Nepomuceno EM, Tucker SJ 2007 Successful treatment of metastatic androgen-independent prostate carcinoma in a transsexual patient. *Clin Genitourin Cancer* 5:344–346
135. Thurston AV 1994 Carcinoma of the prostate in a transsexual. *Br J Urol* 73:217
136. van Haarst EP, Newling DW, Gooren LJ, Asscheman H, Prenger DM 1998 Metastatic prostatic carcinoma in a male-to-female transsexual. *Br J Urol* 81:776
137. 2008 Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 149:185–191
138. Futterweit W 1998 Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav* 27:209–226
139. Miller N, Bédard YC, Cooter NB, Shaul DL 1986 Histological changes in the genital tract in transsexual women following androgen therapy. *Histopathology* 10:661–669
140. O'Hanlan KA, Dibble SL, Young-Spint M 2007 Total laparoscopic hysterectomy for female-to-male transsexuals. *Obstet Gynecol* 110:1096–1101
141. Chadha S, Pache TD, Huikeshoven JM, Brinkmann AO, van der Kwast TH 1994 Androgen receptor expression in human ovarian and uterine tissue of long-term androgen-treated transsexual women. *Hum Pathol* 25:1198–1204
142. Dizon DS, Tejada-Berges T, Koelliker S, Steinhoff M, Granai CO 2006 Ovarian cancer associated with testosterone supplementation in a female-to-male transsexual patient. *Gynecol Obstet Invest* 62:226–228
143. Hage JJ, Dekker JJ, Karim RB, Verheijen RH, Bloemena E 2000 Ovarian cancer in female-to-male transsexuals: report of two cases. *Gynecol Oncol* 76:413–415
144. Mueller A, Gooren L 2008 Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol* 159:197–202
145. Selvaggi G, Ceulemans P, De Cuypere G, Van Landuyt K, Blondeel P, Hamdi M, Bowman C, Monstrey S 2005 Gender identity disorder: general overview and surgical treatment for vaginoplasty in male-to-female transsexuals. *Plast Reconstr Surg* 116:135e–145e
146. Tugnet N, Goddard JC, Vickery RM, Khoosal D, Terry TR 2007 Current management of male-to-female gender identity disorder in the UK. *Postgrad Med J* 83:638–642
147. Green R 1998 Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res* 10 Suppl 1:S22–S24
148. McNeill EJ 2006 Management of the transgender voice. *J Laryngol Otol* 120:521–523
149. Becking AG, Tuinzing DB, Hage JJ, Gooren LJ 2007 Transgender feminization of the facial skeleton. *Clin Plast Surg* 34:557–564
150. Giraldo F, Esteve I, Bergero T, Cano G, González C, Salinas P, Rivada E, Lara JS, Soriguer F 2004 Corona glans clitoroplasty and urethrapreputial vestibuloplasty in male-to-female transsexuals: the vulval aesthetic refinement by the Andalusia Gender Team. *Plast Reconstr Surg* 114:1543–1550
151. Goddard JC, Vickery RM, Terry TR 2007 Development of feminizing genitoplasty for gender dysphoria. *J Sex Med* 4:981–989
152. Hage JJ, de Graaf FH, Bouman FG, Bloem JJ 1993 Sculpturing the glans in phalloplasty. *Plast Reconstr Surg* 92:157–161; discussion 162
153. Monstrey S, De Cuypere G, Ettner R 2007 Surgery: female-to-male patient. In: Ettner SR, Monstrey S, Eyler AE, eds. *Principles of transgender medicine and surgery*. New York: The Haworth Press; 135–168
154. Chen HC, Gedebo TM, Yazar S, Tang YB 2007 Prefabrication of the free fibula osteocutaneous flap to create a functional human penis using a controlled fistula method. *J Reconstr Microsurg* 23:151–154
155. Liberopoulos EN, Florentin M, Mikhailidis DP, Elisaf MS 2008 Compliance with lipid-lowering therapy and its impact on cardiovascular morbidity and mortality. *Expert Opin Drug Saf* 7:717–725
156. Davis PJ, Spady D, de Gara C, Forgie SE 2008 Practices and attitudes of surgeons toward the prevention of surgical site infections: a provincial survey in Alberta, Canada. *Infect Control Hosp Epidemiol* 29:1164–1166
157. Forbes SS, Stephen WJ, Harper WL, Loeb M, Smith R, Christoffersen EP, McLean RF 2008 Implementation of evidence-based practices for surgical site infection prophylaxis: results of a pre- and postintervention study. *J Am Coll Surg* 207:336–341

EXHIBIT C

Long-Term Observation of 87 Girls with Idiopathic Central Precocious Puberty Treated with Gonadotropin-Releasing Hormone Analogs: Impact on Adult Height, Body Mass Index, Bone Mineral Content, and Reproductive Function

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Objective: We assessed in a retrospective unicenter study the impact of treatment with GnRH analogs (GnRHa) on adult height (AH), body mass index (BMI), bone mineral density (BMD), and reproductive function in girls with idiopathic central precocious puberty (ICPP).

Patients: Eighty-seven ICPP patients were treated with GnRHa for 4.2 ± 1.6 yr (range 3–7.9) and observed for 9.9 ± 2.0 yr (range 4–10.6 yr) after discontinuation of treatment; to estimate the efficacy better, 32 comparable ICPP untreated girls were analyzed.

Results: AH was 159.8 ± 5.3 cm, significantly higher than pretreatment predicted AH (PAH) either for accelerated or for average tables of Bayley and Pinneau. The gain in centimeters between pretreatment PAH and AH was 5.1 ± 4.5 and 9.5 ± 4.6 cm, respectively. Hormonal values and ovarian and uterine dimensions, reduced during treatment, increased to normal after 1 yr without therapy. Age of menarche was 13.6 ± 1.1 yr with an interval of 0.9 ± 0.4 yr after therapy. Menstrual pattern was normal. Six girls became pregnant and delivered normal offspring. BMI *sd* score for chronological age increased, but not significantly, before, during, and after therapy. BMD at discontinuation of treatment was significantly lower and increased to control values after gonadal activity resumption.

Conclusions: GnRHa treatment in ICPP is safe for the reproductive system, BMD, and BMI and helpful in reaching AH close to target height; however, the variability of individual responses suggests that one choose more parameters than increment in height, especially in girls with pubertal onset over 8 yr of age. (*J Clin Endocrinol Metab* 93: 190–195, 2008)

For more than 20 yr (1), GnRH analogs (GnRHa) have been used in the treatment of central precocious puberty (CPP). The question of adult height (AH) improvement is still controversial, although a considerable number of CPP subjects treated with GnRHa for many years have reached AH. Long-term observations during and after discontinuation of therapy and follow-up studies of big cohorts of CPP patients are reported (2–14). In this unicenter retrospective study on a group of 87 girls affected by idiopathic central precocious puberty (ICPP) treated with GnRHa and observed for several years after discontinua-

tion of treatment, we evaluated the impact on AH, body mass index (BMI), bone mineral density (BMD), and reproductive function.

Subjects and Methods

Subjects

Eighty-seven girls with ICPP were treated with GnRHa for 4.2 ± 1.6 yr (range 3–7.9) and observed for 9.9 ± 2.0 yr (range 4–10.6) after discontinuation of treatment (Tables 1 and 2).

Abbreviations: AH, Adult height; BA, bone age; BMD, bone mineral density; BMI, body mass index; CA, chronological age; CPP, central precocious puberty; GnRHa, GnRH analogs; ICPP, idiopathic CPP; MRI, magnetic resonance imaging; PAH, predicted adult height; PAH-BP, PAH using tables for accelerated girls; PAH-BPav, PAH using tables for average girls; SDS, *sd* score; TH, target height; vBMD, volumetric BMD.

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TABLE 1. Clinical and auxological characteristics of CPP patients at the start and end of treatment and AH

Parameter	Treated group (n = 87)	Untreated group (n = 32)
Before treatment		
CA at first observation (yr)	6.5 ± 1.5	6.8 ± 1.6
BA at first observation (yr)	9.1 ± 2.3	9.1 ± 1.0
CA at start of treatment (yr)	8.4 ± 1.5	8.3 ± 1.2
BA at start of treatment (yr)	11.1 ± 1.6	11.2 ± 1.4
Height velocity before treatment (cm/yr)	8.2 ± 1.8	
BMI (kg/m ²)	18.5 ± 2.4	
BMI SDS for CA	0.39 ± 0.8	
Height SDS-BA	−1.2 ± 0.8	−1.1 ± 0.6
Height (cm)	134.8 ± 9.3	136.0 ± 8.9
PAH-BPav (cm)	150.0 ± 5.1	151.0 ± 3.9
PAH-BP (cm)	154.2 ± 5.2	155.1 ± 4.3
At end of treatment		
CA (yr)	12.6 ± 1.0	
BA (yr)	13.1 ± 0.5	
BMI (kg/m ²)	21.7 ± 3.1	
BMI SDS for CA	0.41 ± 0.9	
Height SDS-BA	−0.2 ± 0.8 ^a	
Height (cm)	153.8 ± 5.0	
PAH-BPav (cm)	160.6 ± 5.9 ^a	
PAH-BP (cm)	162.8 ± 6.6 ^a	
Duration of treatment (yr)	4.2 ± 1.6	
At adult height		
CA (yr)	16.1 ± 2.2	16.3 ± 2.7
BA (yr)	16.0 ± 1.5	17.7 ± 2.7
BMI (kg/m ²)	22.9 ± 3.8 ^b	
BMI SDS for CA	0.44 ± 1.0	
Height SDS-BA	−0.5 ± 0.9 ^a	−1.3 ± 1.0 ^c
Adult height (cm)	159.8 ± 5.3 ^d	154.4 ± 5.9 ^e
Target height (cm)	157.6 ± 4.7	158.5 ± 4.8
ΔAH-PAH-BPav at start (cm)	9.5 ± 4.6	3.0 ± 6.0 ^c
ΔAH-PAH-BP at start (cm)	5.1 ± 4.5	0.6 ± 4.5 ^c
ΔAH-final height (cm)	5.6 ± 2.6	
ΔAH-TH (cm)	2.4 ± 5.2	−4.3 ± 5.7 ^c

Values are the mean ± SD.

^a $P < 0.001$.

^b $P < 0.01$ vs. start of GnRHa.

^c $P < 0.001$.

^d $P < 0.01$, AH vs. TH.

^e $P < 0.01$, treated group vs. nontreated group.

Diagnosis of CPP was made according to the following classical criteria: 1) onset of breast development (stage B2 or above according to Tanner) before 8 yr of chronological age (CA), 2) pubertal LH response (>7 IU/liter) to GnRH stimulation test, 3) increment of height velocity and advancement of bone age (BA) by at least 1 yr over CA, 4) uterine length greater than 3.5 cm and ovarian volumes greater than 1.5 cm³ at ultrasound. No evidence of hypothalamic-pituitary organic lesions at magnetic resonance imaging (MRI) allowed us to classify as idiopathic the CPP of these girls. However, throughout the years, MRI was repeated to confirm the initial findings. We repeated MRI in the youngest subjects and those with particularly progressive clinical picture before treatment without following a rule in number and frequency.

Personal history, rate of pubertal progression, and consequent psychological problems were evaluated since the first observation. CA at initial evaluation was 6.5 ± 1.5 yr (range 1.2–7.9), BA was 9.1 ± 2.3 yr (range 2–11). Although CA at initial evaluation was generally older than CA at appearance of the first signs of puberty because this is reported by

relatives and generally quite not sufficiently documented, we decided not to consider for statistical evaluation CA at onset of puberty but CA at first observation.

The initial evaluation included measuring height, pubertal stage, BA, basal plasma estradiol levels, and LH and FSH responses to GnRH test. In girls presenting with pubic hair as first sign of puberty and striking advancement of BA, an ACTH iv test was performed to evaluate basal and after stimulation 17α -hydroxyprogesterone and testosterone levels to exclude the possibly underlying coexistence of nonclassical congenital adrenal hyperplasia.

GnRHa treatment was undertaken after an observation period of at least 6 months to rule out transient or slowly progressive forms of CPP. Patients were treated with depot triptorelin (D-TRP6-LHRH) at a dose of 100–120 μ g/kg every 21–25 d im. Cyproterone acetate was given orally at the dose of 100 mg/d, divided into two administrations, for 21 d before and 21 d after the first GnRH analog injection to prevent any stimulatory effect by gonadotropins during this flare-up period. The dose was reduced to 50 mg/d the last week.

CA at the start of therapy was 8.4 ± 1.5 yr (range 1.7–9.5), BA was 11.1 ± 1.6 yr (range 3–12), respectively.

Height, weight, BA, pubertal staging, and LH and FSH levels after standard GnRH test were evaluated every 6 months during treatment to assess the suppression of the pituitary-gonadal axis. The dose of GnRHa was adjusted to maintain complete suppression of the pituitary-gonadal axis, demonstrated by GnRH test and after the change of body weight along treatment.

The girls discontinued treatment at a CA of 12.6 ± 1.0 yr (range 10.2–13.5) and at a BA of 13.1 ± 0.5 yr (range 12–14.2).

During the observation period subsequent to the cessation of therapy, all the girls reached AH. AH was considered to be reached when during the preceding year growth was less than 1 cm with a BA of over 15 yr.

BMI of each subject was calculated before, during, and after treatment (even after more than 5 yr) to verify significant changes.

BMD was evaluated at discontinuation of therapy and yearly afterward.

As to reproductive function, during treatment, FSH and LH levels, uterine length, and ovarian volumes at ultrasound were evaluated every 6 months. After discontinuation of treatment, the resumption of menarche, menstrual cycles, underachievement of pregnancy, and birth of a fetus were documented.

To estimate the treatment efficacy better, we analyzed 32 contemporary untreated girls comparable with those treated (Table 1). These patients had refused GnRHa treatment for several reasons, although continuing to remain under observation.

Methods

At each evaluation, height was measured three times by the same observer with a Harpenden's stadiometer. Pubertal staging was calculated by the standards of Marshall and Tanner (15). BA was determined according to the atlas of Greulich and Pyle (16) by the same two observers. Predicted adult height (PAH) was calculated according to the method of Bayley and Pinneau (17) twice for each patient, as follows: the tables for accelerated girls, in which BA is advanced for CA by 1 yr or more (PAH-BP) and the tables for average girls, in which BA is within 1 yr of CA (PAH-BPav), which was used in all the patients as suggested by Kauli *et al.* (18) also the tables for average girls, disregarding how advanced BA was, in each girl.

Target height (TH) was calculated as midparental height adjusted for sex (minus 6.5) (19).

BMI was calculated as weight (kilograms)/height (square meters) and was expressed in SD score (SDS) for CA, according to Cacciari *et al.* (20)

BMD was measured by dual-energy x-ray absorptiometry in the lumbar spine at the L2–L4 level, a site that provides by a measure of integral (cortical plus trabecular) bone, with a QDR 4500 densitometer (Hologic, Bedford, MA). The values were corrected by the vertebral surface scanned and expressed as BMD (grams per square centimeter). Dual-energy x-ray absorptiometry-derived data were used to calculate lumbar spine volumetric BMD (vBMD), expressed in grams per cubic centimeter,

TABLE 2. Clinical and auxological characteristics of group 1 (CA ≤ 7 yr at first observation) and group 2 (CA > 7 yr at first observation) at diagnosis, the start, discontinuation of treatment, and AH

Parameter	Treated		P value
	≤7 yr (n = 44)	>7 yr (n = 43)	
Before treatment			
CA at first observation (yr)	5.6 ± 1.6	7.5 ± 0.3	
BA at first observation (yr)	8.1 ± 2.6	10.1 ± 1.3	
CA at start (yr)	7.7 ± 1.6	9.1 ± 0.8	
BA at start (yr)	10.4 ± 1.8	11.7 ± 0.9	
Height SDS-BA	−1.03 ± 0.8	−1.34 ± 0.7	NS
Height (cm)	133.0 ± 10.3	137.5 ± 5.5	
PAH-BPav (cm)	150.3 ± 5.4	149.7 ± 4.3	NS
PAH-BP (cm)	155.2 ± 5.7	153.2 ± 4.5	NS
TH (cm)	157.1 ± 5.4	158.0 ± 3.9	NS
At end of treatment			
CA (yr)	12.4 ± 1.05	12.8 ± 1.02	NS
BA (yr)	13.0 ± 0.5	13.2 ± 0.5	NS
Height SDS-BA	−0.04 ± 0.8	−0.42 ± 0.8	<0.05
Height (cm)	154.7 ± 4.6	152.8 ± 5.4	NS
PAH-BPav (cm)	162.0 ± 6.1	158.5 ± 6.4	<0.05
PAH-BP (cm)	164.6 ± 6.5	161.1 ± 5.8	<0.05
Treatment (yr)	4.7 ± 1.8	3.7 ± 1.0	<0.005
At AH			
CA (yr)	16.2 ± 2.6	15.8 ± 2.0	NS
BA (yr)	15.9 ± 1.5	15.9 ± 1.5	NS
Height SDS-BA	−0.24 ± 0.9	−0.68 ± 0.8	<0.05
AH (cm)	160.9 ± 5.6	158.6 ± 4.8	NS
ΔAH-PAH-BPav at start (cm)	10.4 ± 4.7	8.6 ± 4.4	NS
ΔAH-PAH-BP at start (cm)	5.6 ± 4.6	4.9 ± 4.3	NS
ΔAH-final height (cm)	5.8 ± 2.7	5.5 ± 2.5	NS
ΔAH-TH (cm)	4.0 ± 5.1	0.75 ± 4.8	<0.01

Data are expressed as mean ± SD.

taking the vertebral body as an ellipsoid cylinder and dividing bone mineral content obtained by lateral scan (in grams) by body vertebral volume (in cubic centimeters), calculated ($p \times \text{width}/2 \times \text{depth}/2 \times \text{height}$) to reduce the confounding effect of bone size (21).

Statistical analysis

Data are expressed as the mean ± SD, unless otherwise stated. Statistical analysis of the results was assessed using Student *t* test, paired and unpaired if required. Correlations between two parameters were determined by Pearson's correlation coefficient analysis. $P < 0.05$ was considered significant.

Results

At first observation, mean CA was 6.5 ± 1.5 and BA 9.1 ± 2.3 yr; at the start of treatment, CA was 8.4 ± 1.5 and BA 11.1 ± 1.6 yr, height was 134.8 ± 9.3 cm, and BMI 18.5 ± 2.4 kg/m². AH, reached after GnRHa treatment for a duration of 4.2 ± 1.6 yr, was 159.8 ± 5.3 cm. Because pretreatment PAH was 154.2 ± 5.3 cm (BP accelerated) and 150.1 ± 5.1 (BP average), the gain obtained with treatment on AH was 5.1 ± 4.5 and 9.5 ± 4.6 cm, respectively. Nevertheless, AH was well above TH ($P < 0.01$). Regression analysis between AH and several parameters (Table 3) showed a positive correlation with TH, height at the initiation and end of treatment, and PAH before and at the end of treatment and no correlation with duration of treatment, in agreement with other authors.

To investigate whether growth results could be influenced by the age at onset of puberty, we divided our patients into two groups: group 1 with CA younger than 7 yr ($n = 44$) and group 2 with CA older than 7 yr ($n = 43$). No significant difference was

TABLE 3. Factors associated with AH (centimeters) in girls treated with GnRHa for precocious puberty

	r	P value
TH	0.411	<0.05
CA at first observation (yr)	−0.268	<0.05
Height at the start of treatment (SDS)	0.588	<0.001
PAH-BP at the start of treatment (cm)	0.558	<0.001
PAH-BPav at the start of treatment (cm)	0.425	<0.01
Duration of treatment	0.252	NS
Height at the end of treatment (SDS)	0.588	<0.001
Growth velocity at the end of treatment (cm/yr)	0.533	<0.001
PAH-BP at the end of treatment (cm)	0.881	<0.001
PAH-BPav at the end of treatment (cm)	0.558	<0.001
ΔAH-height at the end of treatment (cm)	0.361	<0.001

found between the two groups as to AH or the gain in centimeters over PAH (Table 2).

The comparison between AH of the 87 treated girls and 32 ICPP comparable untreated girls, who served as control group, although not randomized, showed that the untreated subjects had a significant loss in terms of centimeters *vs.* treated girls' AH (5.4 cm) *vs.* their TH (4.3 ± 5.7 cm; $P < 0.01$) and *vs.* their average PAH (about 6 cm) and accelerated PAH (about 5 cm; $P < 0.001$; Table 1).

Because BMI in children is age related, either considering the whole group or considering the two groups with onset before or after 7 yr of age, during treatment a marked increase was observed. However, as at the beginning of treatment, BMI SDS for CA was 0.39 ± 0.8 , at discontinuation 0.41 ± 0.9 , and many years after 0.44 ± 1.0 ; no significant difference ($P = \text{NS}$) was found. Not all the patients were overweight or obese (14.3 and 9.1%, respectively, at the start of therapy and 11.7% for both categories either at discontinuation of treatment or several years after at AH).

We observed that, besides individual data, on the whole BMI increased, although remaining in the same centile or SDS throughout treatment. Furthermore, patients who were overweight or obese at the end of treatment were in the same position of the beginning. Regression analysis showed BMI SDS for CA at the end of treatment positively correlated with BMI SDS for CA at the start of treatment ($P < 0.001$; $r = 0.332$).

BMD was evaluated in 66 of 87 patients. At discontinuation of treatment, mean BMD lumbar spine was 0.82 ± 0.01 g/cm² and mean vBMD was 0.135 ± 0.03 g/cm³; both values were significantly lower ($P < 0.001$) than in controls (1.001 ± 0.11 g/cm² and 0.143 ± 0.03 g/cm³, respectively).

At complete resumption of gonadal activity, mean BMD lumbar spine increased to 1.000 ± 0.11 g/cm², not significantly different from controls (1.015 ± 0.11 g/cm²); similarly, mean vBMD increased to 0.165 ± 0.01 g/cm³, not significantly different from controls (0.166 ± 0.02 g/cm³).

Plasma FSH and LH peaks after the LHRH test were suppressed during treatment significantly lower than pretreatment (peak LH 0.6 ± 0.7 *vs.* 24.2 ± 28.3 IU/liter, peak FSH 1.6 ± 1.0 *vs.* 13.2 ± 7.1 IU/liter, both $P < 0.005$); by 1 yr after therapy, peak LH arose back to 30.3 ± 16.0 and FSH to 11.5 ± 11.9 IU/liter ($P < 0.005$). Estradiol basal levels (26.9 ± 5.5 pg/ml) during treatment were significantly lower than pretreatment (8 ± 2.8 pg/ml; $P < 0.001$) and arose to 64.9 ± 13.6 pg/ml 1 yr after therapy withdrawal ($P < 0.001$).

Ovarian volumes, reduced from 2.8 ± 1.3 to 1.9 ± 1.0 cm³ during treatment, increased to 5.4 ± 3.2 cm³ ($P < 0.001$), and uterine length, unchanged during treatment (4.6 ± 0.8 cm), increased to 6.7 ± 0.9 cm ($P < 0.001$), both already after 1 yr without therapy. Menarche appeared at the age of 13.6 ± 1.1 yr after withdrawal of GnRHa at 0.9 ± 0.4 yr (range 0.3–2 yr). The history of menstrual pattern showed that 82 patients had regular menses; the remaining five showed oligomenorrhea due to intensive sport activity, which within 2–3 yr resolved after decrease of intensive exercise. Six girls (one of them twice) became pregnant and delivered normal offspring (Figs. 1 and 2).

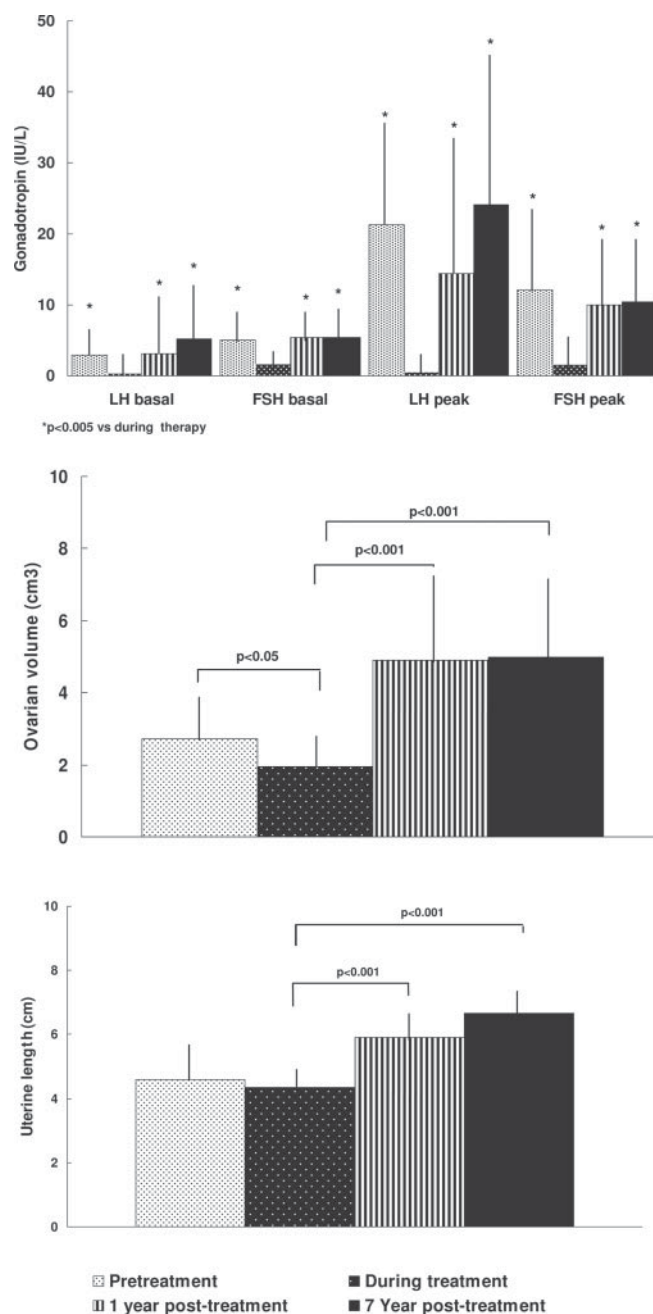


FIG. 1. LH and FSH basal and post-GnRH stimulated levels. Ovarian volume and longitudinal uterine length before treatment, during treatment, and at 1 and 7 yr after treatment in ICPP girls.

Discussion

ICPP is the most frequent cause of CPP in girls aged 6–8 yr (11, 22). Because these patients represent a relatively homogeneous population, it allows a more accurate evaluation of the impact on AH due to the use of GnRHa than in organic CPP.

Our 87 patients, as a whole, reached or overcame TH, and their AH increased significantly *vs.* pretreatment PAH (8, 9). The comparison of AH obtained in treated girls *vs.* AH of the untreated control group shows that in the latter AH is shorter about 5 cm, significantly shorter than 4 cm *vs.* their TH and has no

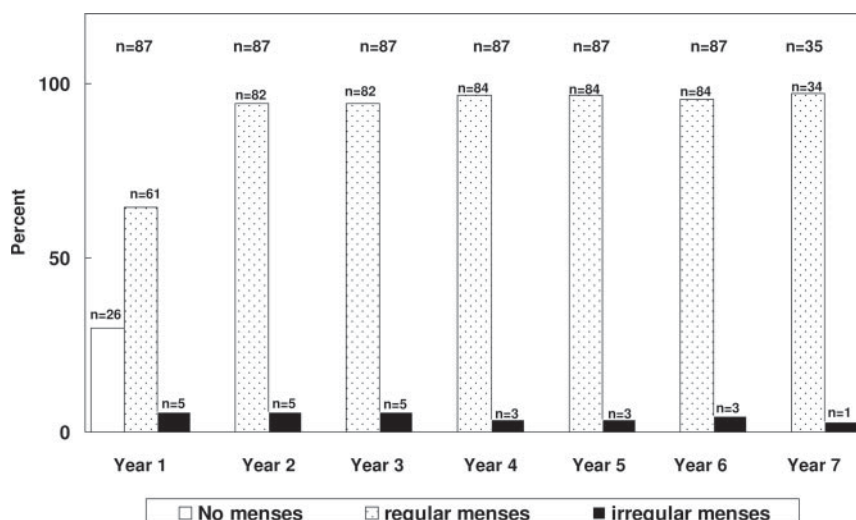


FIG. 2. Patterns of menses at 1, 2, 3, 4, 5, 6, and 7 yr after therapy in girls with ICPP.

significant gain *vs.* their average PAH and no gain *vs.* accelerated PAH.

Our results (7) confirm that there is no significant difference between the gain on AH over PAH pretreatment obtained in girls with onset of puberty less than 7 yr and those with onset over 7 yr. The division in the two groups below and over 7 yr is justified by the fact that in Italy the cutoff of 8 yr in girls is still maintained for the diagnosis of precocious puberty (23). Of course, more striking results are obtained in younger children, younger than 5–6 yr, in whom the potential height should be restored in the range of TH, in view of a severe loss in AH. The extreme variability observed in the growth response of these patients to GnRHa suggests that other factors besides auxological results should be considered when deciding on whether a patient should be treated.

A debated point is still the BMI pattern during and after treatment. Some authors (13, 24, 25) reported a significant increase all along the observation, others (26) even a reduction during the first period. In our cohort, which had a lesser number of overweight or obese children in comparison with other cohorts reported (8, 13, 24), we observed that, besides individual data, on the whole BMI increased, although remaining in the same centile or SDS throughout treatment. Furthermore, patients who were overweight or obese at the end of treatment were in the same position as at the beginning. In conclusion, GnRHa did not result in a significant BMI increment.

As to the bone mineral content, ovarian activity suppression was previously demonstrated to be the cause of BMD reduction, already 1 yr after the beginning of treatment (27–30). We observed, some years after the cessation of therapy, at AH and complete resumption of ovarian activity, that mineral content was totally restored and peak bone mass reached, leading to the conclusion that GnRHa inhibits the acquisition of mineral content in the bone during therapy, but mineral content is restored after therapy (8, 31–33).

No relevant side effects (rash, anaphylaxis) were observed (34). The reactivation of the hypothalamo-pituitary-gonadal axis was prompt and similar for all the patients, as either go-

nadotropin and estrogen levels or completion of uterine and ovarian development; menarche appeared around 1 yr after the end of treatment with regular cycles and six pregnancies with normal offspring, as observed by other authors (8, 13, 14, 24, 35–38).

Because treatment leads to reduction of height velocity, together with bone maturation, in turn influenced by hormonal extragonadal (adrenal), nutritional, and genetic factors and height prediction should be considered with caution for the inaccuracy of methods (13, 14, 39), the increment of statural growth with a gain of some centimeters on AH cannot be reasonably considered the aim of GnRHa therapy. The rate of pubertal progression, psychological problems depending on personal sensitivity, and

the age of onset well below 7 yr, in which the loss of linear growth for years is unavoidable, seem to be the main factors for deciding to treat girls affected by ICPP with GnRHa.

Furthermore, our experience suggests not to establish fixed rules (BA, CA, height velocity slow-down) for discontinuation of therapy. It is better to consider each individual with respect to height satisfaction, compliance, and quality of life, including the need to sexually develop contemporaneously with their peers.

In conclusion, GnRH treatment in ICPP is safe and reversible for the reproductive system, BMD, and BMI. As to growth, it seems to be helpful in reaching an AH close to TH, but the variability of individual response suggests that one choose other parameters than increment in height, especially in girls with pubertal onset over 8 yr of age.

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References

1. Crowley WF, Comite F, Vale W, Rivier J, Loriaux DL, Cutler GB 1981 Therapeutic use of pituitary desensitization with a long-acting LHRH agonist: a potential new treatment for idiopathic precocious puberty. *J Clin Endocrinol Metab* 52:370–372
2. Oerter KE, Manasco P, Barnes KM, Jones J, Hill S, Cutler GB 1991 Adult height in precocious puberty after long-term treatment with deslorelin. *J Clin Endocrinol Metab* 73:1235–1240
3. Kletter GB, Kelch RP 1994 Effects of gonadotropin-releasing hormone analog therapy on adult stature in precocious puberty. *J Clin Endocrinol Metab* 79:331–334
4. Paul D, Conte FA, Grumbach MM, Kaplan SL 1995 Long term effect of gonadotropin-releasing hormone agonist therapy on final and near-final height in 26 children with true precocious puberty treated at a median age of less than 5 years. *J Clin Endocrinol Metab* 80:546–551
5. Oostdijk W, Rikken B, Schreuder S, Otten B, Odink R, Rouwe C, Jansen M, Gerver WJ, Waelkens J, Drop S 1996 Final height in central precocious puberty

- after long term treatment with a slow release GnRH agonist. *Arch Dis Child* 75:292–297
6. Arrigo T, Cisternino M, Galluzzi F, Bertelloni S, Pasquino AM, Antoniazzi F, Borrelli P, Crisafulli G, Wasniewska M, De Luca F 1999 Analysis of the factors affecting auxological response to GnRH agonist treatment and final height outcome in girls with idiopathic central precocious puberty. *Eur J Endocrinol* 141:140–144
 7. Carel JC, Roger M, Ispas S, Tondou F, Lahlou N, Blumberg J, Chaussain JL 1999 Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. *J Clin Endocrinol Metab* 84:1973–1978
 8. Heger S, Partsch C-J, Sippell WG 1999 Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. *J Clin Endocrinol Metab* 84:4583–4590
 9. Antoniazzi F, Arrigo T, Cisternino M, Galluzzi F, Bertelloni S, Pasquino AM, Borrelli P, Osio D, Mengarda F, De Luca F, Tatò L 2000 End results in central precocious puberty with GnRH analog treatment: the data of the Italian Study Group for Physiopathology of Puberty. *J Pediatr Endocrinol Metab* 13(Suppl 1):773–780
 10. Mul D, Oostdijk W, Otten BJ, Rouwe C, Jansen M, Delemarre-van de Waal HA, Waelkens JJJ, Drop SLS 2000 Final height after gonadotrophin releasing hormone agonist treatment for central precocious puberty: the Dutch experience. *J Pediatr Endocrinol Metab* 13:765–772
 11. Klein KO, Barnes KM, Jones JV, Feuillan P, Cutler GB 2001 Increased final height in precocious puberty after long-term treatment with LHRH agonists: the national institutes of health experiences. *J Clin Endocrinol Metab* 86:4711–4716
 12. Adan L, Chemaitilly W, Trivin C, Brauner R 2002 Factors predicting adult height in girls with idiopathic central precocious puberty: implications for treatment. *Clin Endocrinol (Oxf)* 56:297–302
 13. Paterson WF, McNeill E, Young D, Donaldson MDC 2004 Auxological outcome and time to menarche following long-acting goserelin therapy in girls with central precocious or early puberty. *Clin Endocrinol (Oxf)* 61:626–634
 14. Tanaka T, Niimi H, Matsuo N, Fujieda K, Tachibana K, Ohyama K, Satoh M, Kugu K 2005 Results of long-term follow-up after treatment of central precocious puberty with leuporelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function. The TAP-144-SR Japanese Study Group on central precocious puberty. *J Clin Endocrinol Metab* 90:1371–1376
 15. Marshall WA, Tanner JM 1969 Variations in pattern of pubertal changes in girls. *Arch Dis Child* 44:291–303
 16. Greulich WW, Pyle SI 1959 Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford, CA: Stanford University Press
 17. Bayley N, Pinneau SR 1952 Tables for predicting adult height from skeletal age: revised for use with the Greulich and Pyle hand standards. *J Pediatr* 40:423–441
 18. Kauli R, Galatzer A, Kornreich L, Lazar L, Pertzalan A, Laron Z 1997 Final height of girls with central precocious puberty, untreated versus treated with cyproterone acetate or GnRH analogue. *Horm Res* 47:54–61
 19. Tanner JM, Goldstein H, Whitehouse RH 1970 Standards for children's height at ages 2–9 allowing for height of parents. *Arch Dis Child* 45:755–762
 20. Cacciari E, Milani S, Balsamo A, Spada E, Bona G, Cavallo L, Cerutti F, Gargantini L, Greggio N, Tonini G, Cicognani A 2006 Italian cross-sectional growth charts for height, weight and BMI (2 to 20 yr). *J Endocrinol Invest* 29:581–593
 21. Kroger H, Vainio P, Nieminen J, Kotaniemi A 1995 Comparison of different models for interpreting bone mineral density measurements using DXA and MRI technology. *Bone* 17:157–159
 22. Cisternino M, Arrigo T, Pasquino AM, Tinelli C, Antoniazzi F, Beduschi L, Bindi G, Borrelli P, De Sanctis V, Farellò V, Galluzzi F, Gargantini L, Lo Presti D, Sposito M, Tatò L 2000 Etiology and age incidence of precocious puberty in girls: a multicentric study. *J Pediatr Endocrinol Metab* 13(Suppl 1):695–701
 23. Castellino N, Bellone S, Rapa A, Vercellotti A, Binotti M, Petri A, Bona G 2005 Puberty onset in Northern Italy: a random sample of 3597 Italian children. *J Endocrinol Invest* 28:589–594
 24. Palmert MR, Mansfield MJ, Crowley WF, Crigler JF, Crawford JD, Boepple PA 1999 Is obesity an outcome of gonadotropin-releasing hormone agonist administration? Analysis of growth and body composition in 110 patients with central precocious puberty. *J Clin Endocrinol Metab* 84:4480–4488
 25. Traggiai C, Polo Perucchin P, Zerbini K, Gastaldi R, De Biasio P, Lorini R 2005 Outcome after depot gonadotrophin-releasing hormone agonist treatment for central precocious puberty: effects on body mass index and final height. *Eur J Endocrinol* 152:463–464
 26. Arrigo T, De Luca F, Antoniazzi F, Galluzzi F, Segni M, Rosano M, Messina MF, Lombardo F 2004 Reduction of baseline body mass index under gonadotropin-suppressive therapy in girls with idiopathic precocious puberty. *Eur J Endocrinol* 150:533–537
 27. Saggese G, Bertelloni S, Baroncelli GI, Battini R, Franchi G 1993 Reduction of bone density: an effect of gonadotropin releasing hormone analogue treatment in central precocious puberty. *Eur J Pediatr* 152:717–720
 28. Verrotti A, Chiarelli F, Montanaro AF, Morgese G 1995 Bone mineral content in girls with precocious puberty treated with gonadotropin-releasing hormone analog. *Gynecol Endocrinol* 9:277–281
 29. Antoniazzi F, Bertoldo F, Zamboni G, Valentini R, Sirpresi S, Cavallo L, Adami S, Tatò L 1995 Bone mineral metabolism in girls with precocious puberty during gonadotrophin-releasing hormone agonist treatment. *Eur J Endocrinol* 133:412–417
 30. Boot AM, de Muinck-Keizer-Schrama SMPF, Pols HAP, Krenning EP, Drop SLS 1998 Bone mineral density and body composition before and during treatment with gonadotropin-releasing hormone agonist in children with central precocious and early puberty. *J Clin Endocrinol Metab* 83:370–373
 31. Bertelloni S, Baroncelli GI, Sorrentino MC, Perri G, Saggese G 1998 Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *Eur J Pediatr* 157:363–367
 32. Antoniazzi F, Bertoldo F, Lauriola S, Sirpresi S, Gasperi E, Zamboni G, Tatò L 1999 Prevention of bone demineralization by calcium supplementation in precocious puberty during gonadotropin-releasing hormone agonist treatment. *J Clin Endocrinol Metab* 84:1992–1996
 33. Van der Sluis IM, Boot AM, Krenning EP, Drop SLS, de Muinck Keizer-Schrama SMPF 2002 Longitudinal follow-up of bone density and body composition in children with precocious or early puberty before, during and after cessation of GnRH agonist therapy. *J Clin Endocrinol Metab* 87:506–512
 34. Tonini G, Lazzarini M 2000 Side effects of GnRH analogue treatment in childhood. *J Pediatr Endocrinol Metab* 13(Suppl 1):795–803
 35. Manasco PK, Pescovitz OH, Feuillan PP, Hench KD, Barnes KM, Jones J, Hill SC, Loriaux DL, Cutler Jr GB 1988 Resumption of puberty after long term luteinizing hormone-releasing hormone agonist treatment of central precocious puberty. *J Clin Endocrinol Metab* 67:368–372
 36. Jay N, Mansfield MJ, Blizzard RM, Crowley WF, Schoenfeld D, Rhubin L, Boepple PA 1992 Ovulation and menstrual function of adolescent girls with central precocious puberty after therapy with gonadotropin-releasing hormone agonists. *J Clin Endocrinol Metab* 75:890–894
 37. Feuillan PP, Jones JV, Barnes K, Oerter-Klein K, Cutler GB 1999 Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. *J Clin Endocrinol Metab* 84:44–49
 38. Arrigo T, De Luca F, Antoniazzi F, Galluzzi F, Iughetti L, Pasquino AM, Salerno MC, Marseglia L, Crisafulli G 2007 Menstrual cycle pattern during the first gynaecological years in girls with precocious puberty following gonadotropin-releasing hormone analogue treatment. *Eur J Pediatr* 166:73–74
 39. Carel JC, Lahlou N, Roger M, Chaussain JC 2004 Precocious puberty and statural growth. *Hum Reprod Update* 10:135–147

EXHIBIT D

A FOLLOW-UP STUDY OF BOYS WITH GENDER IDENTITY DISORDER

by

Devita Singh

A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy

Department of Human Development and Applied Psychology
Ontario Institute for Studies in Education
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A Follow-up Study of Boys with Gender Identity Disorder

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Department of Human Development and Applied Psychology
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2012

Abstract

This study provided information on the long term psychosexual and psychiatric outcomes of 139 boys with gender identity disorder (GID). Standardized assessment data in childhood (mean age, 7.49 years; range, 3–12 years) and at follow-up (mean age, 20.58 years; range, 13–39 years) were used to evaluate gender identity and sexual orientation outcome. At follow-up, 17 participants (12.2%) were judged to have persistent gender dysphoria. Regarding sexual orientation, 82 (63.6%) participants were classified as bisexual/homosexual in fantasy and 51 (47.2%) participants were classified as bisexual/homosexual in behavior. The remaining participants were classified as either heterosexual or asexual. With gender identity and sexual orientation combined, the most common long-term outcome was desistence of GID with a bisexual/homosexual sexual orientation followed by desistence of GID with a heterosexual sexual orientation. The rates of persistent gender dysphoria and bisexual/homosexual sexual orientation were substantially higher than the base rates in the general male population. Childhood assessment data were used to identify within-group predictors of variation in gender identity and sexual orientation outcome. Social class and severity of cross-gender behavior in childhood were significant predictors of gender identity outcome. Severity of childhood cross-gender behavior was a significant predictor of sexual

orientation at follow-up. Regarding psychiatric functioning, the heterosexual desisters reported significantly less behavioral and psychiatric difficulties compared to the bisexual/homosexual persisters and, to a lesser extent, the bisexual/homosexual desisters. Clinical and theoretical implications of these follow-up data are discussed.

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Chapter 1

Introduction

1.1 Rationale for the Study

Gender identity is usually a central aspect of a person's sense of self and, once developed, appears to be less malleable as development progresses (e.g., Egan & Perry, 2001; Ruble, Martin, & Berenbaum, 2006). The development of one's gender identity and, by extension, gender role, is more than a cognitive milestone as it impacts on virtually all aspects of human functioning. In childhood, significant sex differences are seen in such behavioral domains as peer, toy, and activity preferences (e.g., Fagot, Leinbach, & Hagan, 1986; Ruble et al., 2006; Zucker, 2005b). In adolescence and adulthood, significant sex differences are seen in psychosocial domains such as interpersonal relational styles (e.g., Maccoby, 1998) and career choice (e.g., Lippa, 1998, 2005). One can imagine the profound implications on the person whose gender identity development departs from typical pathways and which results in much distress for the individual, a phenomenon that is recognized clinically as Gender Identity Disorder (GID).

Green and Money's (1960) seminal article on boys with "incongruous gender role" was perhaps the first attempt in the literature to label, describe, and characterize the phenotype of young boys who exhibited a pattern of cross-gender behavior. Fourteen years later, Green's (1974) seminal book, "Sexual Identity Conflict in Children and Adults," provided a comprehensive description of children who were "discontent with the gender role expected of them." Since the publication of these early works and, certainly, with the introduction of GID to the psychiatric nomenclature in the third edition of the *Diagnostic and*

Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 1980), tremendous progress has been made in understanding several aspects of this disorder. The phenomenology of GID is now fairly well documented (e.g., Cohen-Kettenis & Pfäfflin, 2003; Zucker, 2000, 2005a; Zucker & Bradley, 1995) and psychometrically robust assessment measures and procedures have been developed to allow for thorough diagnostic evaluation (for reviews, see Zucker, 1992, 2005b; Zucker & Bradley, 1995).

There are, however, some important gaps in the literature on children with GID, two of which are addressed in the current study. Although the natural history or outcome of boys with GID has received some empirical attention, the findings have not been consistent. Studies have generally found that not all boys with GID persist in having GID in adulthood and, in fact, the majority desist and have a homosexual sexual orientation. However, the rates of persistence of GID found across various studies have been variable, ranging from 2.3% to 30% (Green, 1987; Wallien & Cohen-Kettenis, 2008), but are considerably higher than the estimated prevalence of GID in the general population (Zucker & Lawrence, 2009). The reasons for this variability are a matter of conjecture as little is known about the factors that influence GID persistence into adolescence and adulthood. Further complicating the picture is the finding that some children with GID do grow up to have a heterosexual sexual orientation (e.g., Wallien & Cohen-Kettenis, 2008). Thus, given the variation observed in the long-term gender identity and sexual orientation outcome of boys with GID, it is important to examine childhood predictors of outcome in a sample of boys with atypical gender development. Second, very little is known about the long-term psychiatric outcome of boys with GID as the follow-up studies to date have primarily examined gender identity and sexual orientation outcomes.

The present study aimed to fill these gaps in the literature on boys with GID. First, the study examined the gender identity and sexual orientation outcome of boys with GID. Second, the study examined psychiatric outcome at follow-up. Third, using the extensive assessment data collected during childhood, in conjunction with the follow-up data, the study attempted to identify within-group childhood characteristics that were predictive of variations in gender identity and sexual orientation outcome in adolescence and adulthood.

This chapter will begin with a review of relevant psychosexual terminology. Information about the phenomenology of GID in children, adolescents and adulthood is summarized, including associated psychopathology in children, adolescents, and adults with GID. Current controversies in the field, particularly with regard to diagnosis and treatment, are summarized. This is followed by the results of studies that have examined gender identity and sexual orientation outcome in boys with GID. The literature on the relationship between childhood sex-typed behavior and sexual orientation in adulthood is reviewed. The remainder of the chapter includes a conceptual framework for the study within the field of developmental psychopathology. The chapter concludes with the rationale and goals for the present study. Given that the present study was a follow-up of boys with GID, the literature summarized in this chapter is primarily on that of boys with GID.

1.2 Terminology

1.2.1 *Sex and Gender*

The terms *sex* and *gender* have been used interchangeably in the literature (Muehlenhard & Peterson, 2011). In this thesis, *sex* refers to whether a person is biologically male or female. Some of the common attributes that distinguish a person as male or female include the sex chromosomes, gonads, and internal and external genitalia (Vilain, 2000). *Gender* refers to

psychological and behavioral characteristics associated with males and females (Kessler & McKenna, 1978; Ruble et al., 2006).

1.2.2 Gender Role

The term *gender role*, originally coined by Money (1955), refers to those behaviors, attitudes, and personality attributes that are consistent with cultural definitions and expectations of masculinity and femininity (Diamond, 2002; Zucker & Bradley, 1995). During childhood, gender role is commonly operationalized according to certain observable behaviors, referred to as sex-typed behaviors, including peer preference, interest in rough-and-tumble play, dress-up play, toy preference, and so on (Ruble et al., 2006). These gender role/sex-typed behaviors are often construed as indirect markers of a child's gender identity as they are, on average, sex dimorphic (Zucker, 2005b). For example, boys tend to be more active than girls and engage more in rough-and-tumble play (Maccoby, 1998). Boys, on average, prefer to play with toy vehicles and weapons while girls, on average, prefer to play with dolls and toy household items (Berenbaum & Snyder, 1995). The diagnostic criteria for GID are defined, in part, by a profound and pervasive non-conformity to sex-typed behaviors (American Psychiatric Association, 2000). In children, quantitative measurement of sex-typed behavior is obtained through parent-report questionnaires as well as direct observation (Zucker, 2006a; Zucker & Bradley, 1995). In adolescents and adults with GID, descriptions of these childhood behaviors are obtained through retrospective self-report.

1.2.3 Gender Identity

Gender identity refers to a person's basic sense of self as a male or female, that is, the inner experience of belonging to one gender (Fagot & Leinbach, 1985; Stoller, 1964). Most individuals develop a gender identity that is congruent with their biological sex, such that most

biological females have a “female” gender identity and most biological males have a “male” gender identity. From a cognitive-developmental standpoint, gender identity refers to a child’s ability to not only accurately discriminate males from females, but to also correctly identify his or her own gender status as a boy or a girl. Within this framework, the development of gender identity is a cognitive milestone and is thought to represent the first stage in achieving gender constancy, that is, the understanding that being male or female is a biological characteristic and cannot be changed by altering superficial attributes, such as hair style or clothing (Fagot & Leinbach, 1985).¹ In typically developing children, gender identity is established by age 3, at which point children can correctly answer the question, “Are you a boy or are you a girl?” Gender constancy is, on average, established by age 7. The development of a gender identity carries affective significance, as evidenced by the intensity of children’s “emotional commitment to doing what boys and girls are supposed to do” (Fagot & Leinbach, 1985, p. 687). It is also evidenced by the pride with which young children announce their gender and the embarrassment experienced if they are mislabelled by others (Zucker, 2005c).

1.2.4 Gender Dysphoria

The term *gender dysphoria* refers to the subjective experience of dissatisfaction and discontent about one’s biological status as male or female (Fisk, 1973; Zucker, 2006a). The concept of gender dysphoria is fundamental to clinical work with children, adolescents, and adults with GID as it captures the distress that results from the incongruity between one’s biological/assigned sex and internal experience of gender identity (Cohen-Kettenis & Gooren, 1999; Cohen-Kettenis & Pfäfflin, 2003; Money, 1994). In the DSM-IV criteria for GID (Appendix A), Criterion A1 (“repeatedly stated desire to be, or insistence that he or she is, the

¹ However, individuals who complete sex reassignment challenge this conceptualization of gender identity. These individuals alter surface attributes of gender, such as hair and clothing, as part of their gender role change.

other sex”) can be considered the most concrete and direct expression of gender dysphoria (Zucker, 2010a). There are, however, developmental influences on the way in which children, adolescents and adults express their gender dysphoria. Cognitive development, language capacity, and social desirability are among some of the factors that may influence an individual’s expression of gender dysphoria.

Young children may actually state that they are members of the opposite sex (Cohen-Kettenis & Pfäfflin, 2003; for case examples, see Zucker, 1994; Zucker & Green, 1992). Although this misclassification could be related to the child’s age and cognitive development, it may also reflect the severity of the gender dysphoria if the child does truly believe he/she is of the opposite gender. However, most children with GID do not generally misclassify their sex and they know that they are male or female. Thus, when asked, “Are you a boy or a girl,” they answer correctly (Zucker et al., 1993); however, they will voice the desire to be of the opposite sex and find little that is positive about their own sex (Zucker & Green, 1992). Some children may express the wish to be of the opposite sex (i.e., implying that they know which sex they belong to) and simultaneously insist that they are of the opposite sex (e.g., Zucker, 2000, 2006c). These children may have confusion over gender constancy and may be uncertain whether changing aspects of one’s behavior (e.g., hair, clothing) will also change one’s gender. In fact, young children with GID demonstrate more cognitive confusion about gender compared to controls and appear to have a “developmental lag” in their gender constancy acquisition (Zucker et al., 1999).

There is some evidence that overt statements to be of the opposite sex tend to diminish with age. Older children with GID may not verbalize the wish to be of the opposite sex, perhaps for social desirability reasons (Bates, Skilbeck, Smith, & Benter, 1974). For example, they may

have received feedback directly or indirectly from parents and peers regarding the appropriateness of their cross-gender wish (Bradley, 1999; Zucker & Bradley, 2004). During clinical evaluation, it is not uncommon for older children who are struggling with their gender identity to not endorse the desire to be of the opposite sex, but later in therapy reveal their cross-gender wishes once they have developed feelings of security in the therapeutic relationship. Indeed, during the preparation phase for the DSM-IV, this clinical observation served as the rationale for collapsing of the verbalized wish to be of the other sex with the other behavioral indicators of cross-gender identification (Bradley et al., 1991). In the DSM-III, the desire to be or insistence that one is of the opposite sex was a required criterion for the diagnosis. Zucker and Bradley (1995) conducted a re-analysis of data from Green's (1987) follow-up study of effeminate boys and found some research data to support this clinical observation. Of the 60 boys seen in childhood for effeminate behavior, 47 were 3-9 years old and the remaining 13 were 10-12 years old. Of the 47 younger boys, 43 (91.5%) were reported by their mothers to occasionally or frequently state the wish to be a girl, compared to 9 (69.2%) of the boys in the older age group.

That overt statements to be of the opposite sex tend to diminish with age may not be a cross-national observation in children with GID. Wallien et al. (2009) compared a sample of children with GID seen at a specialized gender clinic in Toronto to a sample of children with GID seen at a gender clinic in the Netherlands on the Gender Identity Interview, which is a self-report measure of cognitive and affective gender identity confusion. An age effect was found for the Toronto patients such that the youngest children in the sample (5 years of age and younger) reported more cross-gender feelings than did the older children (6-12 years). In contrast, there was no significant association between age and scores on the Gender Identity Interview for the

Dutch patients. Thus, in the Dutch sample, older patients were as likely to report cross-gender feelings as younger patients.

For developmental reasons, there are limitations on children's ability to think abstractly about gender and to evaluate the meaning of their gender dysphoria. It is not uncommon that when asked to list reasons for wanting to be of the opposite sex, young children with GID will provide concrete advantages. As an example, one 8-year old boy with GID asserted that it would be better to be a girl because they have better bands, such as the Spice Girls (Zucker & Bradley, 2004). The extent to which a child engages in sex-typed behaviors typical of the opposite sex and their rejection of activities and clothing typical of their own sex can be construed as surface indicators of gender dysphoria. Some children may experience discomfort with their sexual anatomy, which serves as another indicator of their felt gender dysphoria.

Adolescents and adults with GID are generally more straightforward than children in their expression about their unhappiness with their biological sex. In adolescents and adults with GID, verbalization of an intense discomfort with both primary and secondary sex characteristics and the desire for medical treatment (e.g., hormonal treatment, sex reassignment surgery) to address this discomfort is one of the most salient ways in which gender dysphoria is expressed (Cohen-Kettenis & Pfäfflin, 2010; Zucker, 2010a). However, the experience of gender dysphoria does not necessarily imply a desire for sex-reassignment surgery as some adolescents are only interested in hormonal treatment for their gender dysphoria (Cohen-Kettenis & Pfäfflin, 2010). Compared to children, adolescents and adults with GID, on average, have the cognitive and language capacity to think abstractly about their gender identity and gender subjectivity (i.e., beyond surface behaviors) and dialogue about the meaning of their dysphoria and its genesis. They are also more capable of discussing their anatomic dysphoria, which is often at the core of

their distress (Bower, 2001). In such discussions, it is not uncommon for these individuals to express feeling trapped or having been born in the wrong body (e.g., Shaffer, 2005).

1.2.5 Sexual Orientation

Sexual orientation refers to a person's erotic responsiveness to sexual stimuli and is typically measured along the dimension of the sex of the person to whom one is sexually attracted, that is, whether one is attracted to a member of the opposite sex (heterosexual sexual orientation), the same sex (homosexual sexual orientation), or both sexes (bisexual sexual orientation) (LeVay, 1993; Zucker, 2006a; Zucker & Bradley, 1995). Individuals who do not experience sexual attraction are referred to as asexual. Sexual orientation is often assessed with regard to at least two parameters: sexual orientation in fantasy and sexual orientation in behavior (Diamond, 1993; Green, 1987; Sell, 1997). The former refers to erotic fantasies experienced during sexually stimulating events, such as masturbation or while watching erotic pictures or movies, and the latter refers to actual sexual behavior, such as kissing and intercourse.

In contemporary sexology, the assessment of sexual orientation may include psychophysiological techniques to measure sexual arousal (Chivers, Rieger, Latty, & Bailey, 2004), semi-structured interviews (Kinsey, Pomeroy, & Martin, 1948), and self-report questionnaires (e.g., Zucker et al., 1996). From the foregoing definitions, that gender identity and sexual orientation are distinct constructs is obvious, yet, unfortunately, these terms are often conflated (for discussion, see Drescher, 2010b). As discussed later, synonymous use of these terms has implications for how one conceptualizes therapeutic approaches to help children with gender dysphoria feel more comfortable about their biological sex.

1.2.6 Sexual Identity

Sexual identity refers to an individual's experience and conception of their sexual attraction (Diamond, 2000). Thus, it is the individual's recognition, definition/labelling, and acceptance of themselves as heterosexual, bisexual, or homosexual (Diamond, 2002; Savin-Williams & Diamond, 2000). It is important to uncouple the construct of sexual orientation from the construct of sexual identity as they are not always synonymous. For example, a person may be predominantly sexually aroused by homosexual stimuli but may not necessarily regard or accept himself as "homosexual" (e.g., Bailey, 2009; LeVay, 2011; Ross, 1983).

1.2.7 Transgender and Transsexualism

The word *transgender* is an informal (i.e., non-diagnostic) term broadly used to subsume expressions of gender variance or gender nonconformity regardless of whether criteria for GID are met. Typically, individuals who are considered transgendered exhibit significant cross-gendered behaviors or identity. Some adolescents and adults use the term as a self-label of their gender identity (e.g., "I am transgendered" or "I am a trans person") (Lawrence & Zucker, 2012). The term does not imply a particular sexual orientation (Drescher, 2010b).

Transsexualism, used sometimes synonymously with GID in adolescents and adults (e.g., Cohen-Kettenis & Pfäfflin, 2003; Simon, Zsolt, Fogd, & Czobor, 2011), is not an official diagnostic category in the DSM-IV (APA, 2000), although it is a diagnosis in the ICD-10 classification system that is given to adolescents and adults (World Health Organization, 1993). The term *male-to-female transsexual* (MtF) refers to biological males who identify as and desire to live (or are actually living) as females, but does not imply degree of transition to the female gender role (e.g., presenting socially, taking cross-sex hormones, received some type of surgical intervention) (Cohen-Kettenis & Gooren, 1999).

1.3 Phenomenology of Gender Identity Disorder

1.3.1 GID in Children

Although GID was only first introduced to the psychiatric nomenclature in the third edition of the DSM (American Psychiatric Association, 1980), its historical background extends over 150 years ago with case descriptions of individuals who experienced conflict over what is now referred to as their gender identity (see Zucker & Bradley, 1995). The incipient DSM-III diagnoses, Gender Identity Disorder of Childhood and Transsexualism, have since been modified into one overarching diagnosis, Gender Identity Disorder, with distinct criteria sets for children versus adolescents and adults, which reflect developmental variations in clinical presentation. In the present revised fourth edition of the DSM, the diagnosis (Appendix A) requires the presence of two components: (1) evidence of a strong and persistent cross-gender identification, which is generally manifested as the desire to be, or insistence that one is, the other sex and/or through the adoption of cross-sex behaviors, and (2) evidence of persistent discomfort with one's biological sex and/or a sense of inappropriateness in the gender role of that sex, which, in males, is manifested through such behaviors as aversion towards rough-and-tumble play (American Psychiatric Association, 2000). The onset of cross-gender behaviors generally occurs during the preschool period, and signs of GID may be visible as early as two years of age (Cohen-Kettenis & Pfäfflin, 2003). Typically, the behavioral signs of GID precede overt statements about feeling like or wanting to be of the opposite sex (Green 1976, 1987). Parents of boys with GID often report that, from the moment their sons could talk, they insisted on wearing their mothers' clothes and shoes and were predominantly interested in girls' toys (Cohen-Kettenis & Gooren, 1999).

The phenomenology of GID in boys has been well-described elsewhere (e.g., Zucker & Bradley, 1995; Zucker & Cohen-Kettenis, 2008; Cohen-Kettenis & Pfäfflin, 2003). Boys with GID experience a strong psychological identification with the other sex, as evidenced by an array of sex-typed behaviors more characteristic of females and a rejection of sex-typed behaviors characteristic of boys (Green, 1976; Zucker & Bradley, 1995). Zucker (2002, 2008a) identified eight categories of sex-typed behavior relevant to the clinical picture of boys with GID: (1) identity statements, (2) dress-up play/cross dressing, (3) toy play, (4) roles in fantasy play, (5) peer relations, (6) motoric and speech characteristics, (7) involvement in rough-and-tumble play, and (8) statements about sexual anatomy. Boys with GID are usually interested in playing with girls' toys, such as Barbie dolls, and are more intrigued by girls' games and activities (e.g., skipping rope) than boys' activities (e.g., hockey). Although they may be equally interested in play as same-aged peers, they tend to dislike and refrain from rough-and-tumble play and gravitate more towards female peers than male peers.

Some boys with GID do not typically object to wearing stereotypically masculine clothing (e.g., pants) in social settings, such as school, but will engage in cross-dressing when the setting is amenable (Zucker, 2010a) while others will insist on wearing female clothing in public and may demonstrate oppositional behavior if allowed to cross-dress only in private (e.g., Ehrensaft, 2011). In a recent approach to treatment of children with GID, some parents and clinicians allow and even encourage gender transition in childhood. Boys with GID treated within this approach demonstrate strong resistance to wearing male-typical clothing. Instead, they insist on dressing socially and privately in female-typical clothing and are allowed to do so as part of their social gender transition (for case examples, see English, 2011; Rosin, 2008; Spiegel, 2008).

In pretend and dress-up play, boys with GID often take on the female role (e.g., a princess or mother). As discussed earlier, some boys with GID express distress about being a boy and having a male body and some will verbalize the wish to be a girl (for clinical examples, see Zucker 2006c, Zucker et al., 2012b). Some boys with GID also experience “anatomic dysphoria,” which is a dislike of one’s genitals. They may verbalize this dislike, attempt to hide their genitals or pretend to have female genitalia (Cohen-Kettenis & Pfäfflin, 2003; Zucker & Bradley, 1995). Indeed, mothers of boys with GID rated their sons as experiencing higher dissatisfaction with their sexual anatomy compared to mothers of clinical and community control boys (Johnson et al., 2004; Lambert, 2009).

On a terminological note, in referring to children with marked cross-gender behavior, some authors avoid formal nosology (i.e., GID) and, instead, use alternative terms such as “gender nonconforming” or “gender variant” on the premise that these terms are less stigmatizing than GID. The issue in using non-standardized terminology is that the populations to which the term refers is less well defined. “Gender variant,” for example, may refer broadly to children who display varying degrees of cross-gender behavior, some of whom may meet diagnostic criteria for GID but others may not. Further complicating matters, it is not always clear in the literature whether “gender variant” was used as an alternative to GID or as a general term to represent all children with marked cross-gender behavior. Some authors, however, use these alternative terms when referring to children in non-clinical samples (e.g., Rieger, Linsenmeier, Bailey, & Gygax, 2008). In these cases, a gender nonconforming boy is one who is relatively feminine or less masculine compared with other boys and a gender conforming boy is one who is relatively unfeminine compared to other boys. In this thesis, GID is used to refer to children who meet criteria for GID and gender atypical/gender nonconforming is used when

referring more broadly to children with marked cross-gender behavior whose GID status is unknown.

1.3.2 GID in Adolescents and Adults

A core characteristic of adolescents and adults with GID is psychological identification with the opposite sex (American Psychiatric Association, 2000). This generally manifests in the verbalization of an intense desire to be a member of the opposite sex. Some adolescents and adults with GID attempt to adopt the social role or “pass” as a member of the opposite sex through alteration of surface level physical attributes such as hair or clothing style. Another core characteristic of adolescents and adults with GID is discomfort with their sexual anatomy (anatomic dysphoria), though this is not experienced by all individuals with GID (American Psychiatric Association, 2000; Bradley & Zucker, 1997). Anatomic dysphoria may manifest as an interest in taking contra-sex hormones and, in some cases, receiving sex reassignment surgery to alter their physical appearance (Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008; Cohen-Kettenis & Pfäfflin, 2003; de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2011a; Smith, van Goozen, & Cohen-Kettenis, 2001; Zucker, Bradley, Owen-Anderson, Kibblewhite, & Cantor, 2008; Zucker, 2006a). Treatment for adolescents with GID typically involves biomedical interventions that facilitate the transition from one gender to another. It is also recommended and, at times, required that the adolescent also engage in psychotherapy, though with a different treatment philosophy compared to psychotherapy for children with GID (Zucker et al., 2011; Zucker, Wood, Singh, & Bradley, 2012a). In general, this approach to treating adolescents and adults with GID is uncontroversial, though there may be cross-clinic/clinician variations in timing of treatment (e.g., minimum age for cross-sex hormones).

1.4 Prevalence of Gender Identity Disorder

More than 25 years ago, Meyer-Bahlburg (1985) characterized GID as a rare phenomenon. While there have been no formal epidemiological studies on the prevalence of GID in children, adolescents, and adults, other lines of evidence suggest that Meyer-Bahlburg's observation still holds true. Information about the prevalence of cross-gender behavior in children has come from studies using the Child Behavior Checklist (CBCL) (Achenbach & Edelbrock, 1983), a parent-report measure of emotional and behavior problems. The CBCL² has two items that measure cross-gender identification, "Behaves like opposite sex" and "Wishes to be of opposite sex," which can be summed (range, 0-4) to provide a composite of gender identity. In a Dutch study of 7526 7-year-old twin pairs from the general population, 4.7% of children had a summed score (across the two items) of 1 or higher (van Beijsterveldt, Hudziak, & Boomsma, 2006). More recently, Steensma, van der Ende, Verhulst, and Cohen-Kettenis (2012) reported on 879 Dutch children (406 boys, 473 girls) from the general population followed prospectively for 24 years. The mean age in childhood was 7.5 years (range, 4-11 years). Fifty one (5.8%) of the 879 children were classified as gender variant (i.e., summed score on gender identity items was 1 or higher), which is similar to the percentage found by van Beijsterveldt et al.

Since the 1960s, a number of studies have reported estimated prevalence rates for GID in adults (for a review, see Zucker & Lawrence, 2009). Rates have varied, in part, depending on the inclusion criteria (e.g., including individuals who have had, at least, hormonal treatment but have not necessarily had any surgical interventions vs. only including individuals who have had sex reassignment surgery). For example, De Cuypere et al. (2007) estimated that 1 in 12,900

² Items are scored based on the past 6 months on a 0-2 scale where 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true.

biological adult males in Belgium have GID, while Weitze and Osburg (1996) estimated a prevalence rate of 1 in 42,000 in Germany. The estimated prevalence rate in most other studies have fallen within this range (i.e., 1/12,900-1/42,000). Based on these estimated rates, it seems reasonable to presume that the prevalence of GID is low. In Steensma et al.'s (2012) prospective study, only 1 (0.1%) of the 879 participants, a biological male, had undergone gender reassignment (cross-sex hormonal treatment and surgery) when followed up in adulthood.

1.5 Treatment of Children with Gender Identity Disorder

At present, there are three general approaches that guide the clinical management of children with GID, each of which rests on its own conceptualization of gender identity development and GID. It is beyond the scope of this thesis to review in detail treatment approaches and the debates surrounding them (for detailed reviews, discussions, and clinical examples see, for example, Dreger, 2009; Stein, 2012; Zucker, 2001a, 2006c, 2007, 2008b; Zucker & Bradley, 1995; Zucker et al., 2012b).

1.5.1 The Therapeutic Model

In one approach, the goals of treatment are: (1) to circumvent the consistently observed sequelae of GID (e.g., ostracism by peers, depression), (2) to help children feel more comfortable with their biological sex, thereby reducing/alleviating gender dysphoria, (3) to increase the likelihood of desistance of GID in adolescence and adulthood, and (4) to alleviate co-occurring socioemotional problems in the child or difficulties within the family dynamic that may play a role in the child's gender confusion (e.g., Meyer-Bahlburg, 2002; Zucker & Bradley, 1995; Zucker et al., 2012b). Dreger (2009) labeled this approach the "therapeutic model," in contrast to the "accommodating" model described below. However, depending on the clinician's theoretical perspective on the etiology of GID, the specific interventions used may vary.

Some clinicians view cross-gender behaviors as a result of inappropriate learning and attempt to extinguish them using principles of behavior therapy (e.g., Reker & Lovaas, 1974). Zucker et al. (2012b) proposed a multifactorial theory in which cross-gender identification is influenced by several factors, including biological, psychosocial, psychological, and psychodynamic variables. Within this framework, a biopsychosocial model of treatment is used to address the underlying factors that contribute to the child's cross-gender identification (e.g., socioemotional problems within the child, family dynamics). In addition to therapy with the child, intervention may also include parent and/or family counselling. Some clinicians use a strictly psychodynamic formulation in which GID is viewed as a defense against distress and anxiety. Thus, psychodynamically informed therapy is used to address the underlying factors that perpetuate this defensive response (Coates & Wolfe, 1997). Regardless of the etiological framework, a common thread among these clinicians is the assumption that it is possible to modify a child's gender identity (e.g., Meyer-Bahlburg, 2002; Zucker, 2008b). In a variation of the therapeutic approach, clinicians in the Netherlands place the emphasis of treatment on concomitant emotional/behavioral problems in the child as well as family dynamics rather than on direct attempts to modify gender identity (Cohen-Kettenis & Pfäfflin, 2003; de Vries & Cohen-Kettenis, 2012). The rationale for this approach is that, if the concomitant problems have contributed to causing or maintaining the gender dysphoria, then the dysphoria will likely disappear by addressing these problems. de Vries and Cohen-Kettenis have recently referred to the approach used in the Netherlands as the "Dutch approach."

Both the Dutch approach as well as that espoused by Zucker et al. (2012b) utilizes a developmental perspective to treatment. When gender dysphoria persists from childhood into adolescence, it is less likely alleviated by psychological intervention and more likely to be

treated by hormonal and surgical interventions (e.g., Cohen-Kettenis & van Goozen, 1997; de Vries et al, 2011a; Zucker, 2006). Thus, the therapeutic approach for adolescents is one that supports transitioning on the grounds that it will lead to better psychosocial adjustment (Zucker et al., 2011, 2012b).

The therapeutic model has faced intense criticism because some clinicians have claimed that, in addition to treating gender dysphoria, they were also preventing homosexuality, which they viewed as disordered (e.g., Rekers, Bentler, Rosen, & Lovaas, 1977). Some critics of the therapeutic model, and of Zucker's approach in particular, view it as "homophobic" and similar to reparative therapy that has been used in attempts to change an individual's sexual orientation (e.g., Pickstone-Taylor, 2003). Most contemporary clinicians emphasize that the goal of treatment is to resolve conflicts associated with the GID, regardless of the child's eventual sexual orientation (Cohen-Kettenis, 2001; Zucker & Cohen-Kettenis, 2008). Moreover, Bradley and Zucker (2003) have explicitly stated that they do not endorse the prevention of homosexuality as a therapeutic goal. However, some parents of children with GID who request treatment do so, in part, because they hope to prevent homosexuality in their child (Zucker, 2008c). The therapeutic approach has also been criticized on the grounds that it does not appreciate the distinction between children with GID (i.e., children with gender dysphoria) and children who show gender-variant behaviors but without concomitant gender dysphoria (e.g., Stein, 2012). Discussed later, this criticism is a reflection of a broader conceptual and diagnostic debate in the field regarding the conflation of GID proper with presumably innocuous cross-gender behavior.

1.5.2 Accommodation Model

A second approach to treatment of GID has been referred to as the "wait and see" or "accommodation model" (Dreger, 2009; Hill, Rozanski, Carfagnini, & Willoughby, 2005).

Within this framework, there is no direct attempt to help the child feel more comfortable about their biological sex or to modify their cross-gender behaviors. Rather, parents are encouraged to support the child's cross-gender behaviors in order to reduce feelings of stigmatization in the child and to promote the child's overall adjustment (Ehrensaft, 2012; Menvielle, 2012; Menvielle & Hill, 2011; Menvielle & Tuerk, 2002;). Ehrensaft (2011), in her case description of a 6-year-old biological male, explained that, essentially, the family and therapist tolerate a state of "not knowing" until the child "unfolds an authentic gender identity and expression," which may or may not be aligned with their biological sex. If a child's "authentic gender self" is not aligned with their biological sex, early social gender transition is then supported (e.g., Ehrensaft, 2012). The accommodation treatment approach is viewed as supportive and accepting of children's authentic gender role expression on the premise that it does not steer children down a particular gender path (e.g., Bocking & Ehrbar, 2005; Hill et al., 2005). It is arguable, however, that by allowing cross-gender behavior, one is, in fact, steering children down a cross-gendered path. More than two decades ago, Green (1987) speculated that boys whose parents do not attempt to discourage cross-sex behavior might be more likely to become transsexuals as adults. Within this treatment approach, there appears to be an assumption that gender identity can change as indicated by the recognition that some children who socially transition at an early age may want to reverse the gender role transition later on (Ehrensaft, 2012; Menvielle, 2012).

1.5.3 Early Transition Approach

A third, more recent, approach takes an extreme stance on childhood cross-gender behavior and has likely been fuelled by changing ideas about what constitutes appropriate expression of gender (Drescher, 2010a). In this model, pre-pubescent children with GID, sometimes as young as 5 years of age, are allowed and encouraged to socially transition from

one gender to another (e.g., Vanderburgh, 2009; see also Brown, 2006; English, 2011; Rosin, 2008; Spiegel, 2008). There is no attempt to decrease cross-gender behavior and identification. A social transition may involve, for example, a biological male using a female name and registering at school as a female (e.g., Saeger, 2006). This approach is partly rooted in the assumption that the onset of cross-gender behavior is an indication of innate (cross) gender identity rather than as a sign of gender confusion or a GID. Further, it is argued that an early transition (i.e., before puberty) may circumvent associated mental health issues seen in individuals with GID (Vanderburgh, 2009). The role of the therapist is to help families navigate aspects of the transition process, such as advocacy within the social setting and educating families about the medical aspects of transitioning.

There are some serious concerns about this approach. The most striking implication of an approach that facilitates early transitioning is that it may steer some children down a transgendered path who might have otherwise not desired to transition as they progress in development. Proponents of the early transitioning model have not addressed how this approach fits conceptually or clinically with the finding that the majority of children with GID show a desistence in adolescence (e.g., Drummond et al., 2008; Green, 1987; Wallien and Cohen-Kettenis, 2008). This is an important issue because an approach that encourages transitioning in childhood assumes that these children would persist in their GID into adolescence, which is not supported by the follow-up studies of children with GID.

There have been no quantitative follow-up studies on children who socially transition in childhood, probably, in part, because this approach is still relatively recent. However, one qualitative study conducted in The Netherlands suggests that socially transitioning children is not without its drawbacks (Steensma, Biemond, Boer, & Cohen-Kettenis, 2011). In this study, 25

adolescents who had met criteria for GID in childhood were interviewed regarding stability/instability of their gender identity from childhood into adolescence, among other things. The results of two adolescent (biological) females are of relevance to this discussion. In childhood, these females were seen and treated as boys by other children and they dressed in male-typical clothing all the time. It is unclear, however, the extent to which these females were socially transitioned (e.g., name and pronoun use). In adolescence, both girls experienced a desistence of their gender dysphoria and wanted to live in the female gender role. Both girls found it a struggle to attempt living in the female role after having lived to some extent in the male gender role. One girl commented, “At high school, I wanted to make a new start. I did not want people to know that I had looked like a boy and had wanted to be a boy in childhood.” While it is arguable that an approach that supports social transition in childhood may be beneficial to children who will turn out to be persisters, it is not the advisable approach for children who will desist. The challenge, however, is the difficulty in predicting the gender identity outcome of very young children with GID (Steensma & Cohen-Kettenis, 2011).

To date, there is no consensus on the best treatment approach for children with GID. This state of affairs has been maintained by the paucity of empirical data on treatment and also, in part, by theoretical disagreements among clinicians about gender identity development and its malleability in childhood. As a point of agreement, proponents of both the therapeutic and accommodation model agree that, if it is apparent that an adolescent is committed to transitioning, the recommended treatment approach is to provide cross-sex hormonal therapy, to be followed by surgery, if desired, in adulthood. Unfortunately, the debate about therapeutics for children is far from over largely because of scant research attention in this area. There have been no rigorous treatment outcome studies on children with GID and, certainly, no randomized

controlled treatment trials that have compared the effects of these therapeutic approaches on gender identity outcome (Bradley & Zucker, 2003; de Vries & Cohen-Kettenis, 2012; Zucker, 2001a). In addition, there have been no studies that compared any of the different treatment approaches for GID to a condition of no treatment. Beyond resolving debate, there is an even more important reason to evaluate treatment approaches. As noted previously, most children with GID seem to desist in their gender dysphoria by adolescence. It remains unknown whether the aforementioned treatment approaches are associated with different long term outcomes (e.g., persistence vs. desistence of GID, general psychiatric functioning, psychosocial adjustment).

1.6 Diagnostic Controversies

GID is arguably one of the most contentious diagnoses in the DSM. A detailed review of the controversies surrounding the diagnosis is beyond the scope of this chapter, but can be found elsewhere (e.g., Bockting, 2009; Bradley & Zucker, 1998; Bryant, 2006; Drescher 2010a, 2010b; Hill et al., 2005; Meyer-Bahlburg, 2010; Wilson, Griffin, & Wren, 2002; Zucker & Bradley, 1995; Zucker, Drummond, Bradley, & Peterson-Badali, 2009). Essentially, one group of critics argue for a reform of the diagnosis while a second group question the legitimacy of GID as a diagnostic category.

1.6.1 Diagnostic Reform

One major criticism of the GID diagnosis is that it fails to differentiate between children who have both cross-gender identity (gender dysphoria) and pervasive cross-gender behaviors from those who show signs of pervasive cross-gender behavior but without the co-occurring unhappiness about their biological sex (i.e., without co-occurring gender dysphoria) (Bockting, 1997). In the current form of the GID diagnosis (Appendix A), the Point A criterion is met if a child has at least 4 of 5 markers of persistent cross-gender identification: the desire to be, or

insistence that one is, of the other sex (Criterion A1) and marked/pervasive cross-gender role behaviors, such as peer and clothing preference (Criteria A2-A5). Critics have argued that Criterion A1 (which is viewed as capturing gender dysphoria) should not be condensed with criteria pertaining to cross-gender behaviors; otherwise, a child may receive a diagnosis of GID through demonstration of cross-gender behaviors but in the absence of gender dysphoria (e.g., Bartlett, Vasey, & Bukowski, 2000; Bockting & Ehrbar, 2005; Hill et al., 2005; Richardson, 1996, 1999; Wilson et al., 2002). The concern is that a diagnosis and subsequent treatment may be harmful to the child (e.g., Langer & Martin, 2004). Presumably, these critics are arguing that the absence of verbal statements of cross-gender identification or wish is an indicator that the child is not gender dysphoric, regardless of the degree of cross-gender behavior. However, as discussed earlier, a child may experience unhappiness with their biological sex but not verbalize it. It is conceptually possible for children to meet diagnostic criteria for GID if they endorse items A2-A5 and also express unhappiness about their sexual anatomy (i.e., anatomic dysphoria, Criterion B), but yet do not make explicit statements of wanting to be of the opposite sex. These children may actually be struggling with their gender identity and, without a diagnosis, the way in which the cross-gendered behaviors are managed may not be in the best interest of the child (Zucker, 2010a). From a clinical standpoint, however, it is not common for a child to express anatomic dysphoria but not verbalize cross-gender identification.

It has been recommended that the diagnostic criteria be revised such that a distinction is made between children who have both cross-gender identification (manifested as explicit statements of wanting to be of the opposite sex) and cross-gender behaviors from children who only demonstrate cross-gender behaviors (e.g., Bartlett et al., 2000). Zucker (2005c) suggested that one solution to this debate is a modification of the DSM-IV diagnostic criteria such that it

would be necessary for the child to systematically verbalize the wish to be of the opposite sex in order for the Point A criterion to be met. In a re-analysis of a parent-report measure of cross-gender identification, Zucker (2010a) found that children who frequently stated the desire to be of the other gender also showed more pervasive cross-gender behaviors. In part because of this finding, the DSM-5 Workgroup on GID has recommended that the persistent desire to be or insistence that one is of the opposite gender should be a necessary criterion for the diagnosis of GID. It is hoped that this change would result in a tightening of the diagnostic criteria and may better separate children with GID from those displaying marked variance in their gender role behaviors but without the desire to be of the other gender. The proposed revision to the DSM-IV diagnostic criteria for GID in children is summarized in Appendix B. The Workgroup on GID proposed retention of the diagnosis in DSM-5 with a name change (“Gender Dysphoria in Children”). In addition to statements of cross-gender identification (Criterion A1), children need to have at least 5 of 7 other manifestations of incongruence between expressed and assigned gender. In the proposed diagnostic criteria, rejection of sex-typical toys, games and activities, and anatomic dysphoria are part of Point A criteria. Point B criteria pertain to distress or impairment.

1.6.2 Is GID a Mental Disorder?

That GID is not a mental disorder and should, therefore, be removed from the DSM has been argued from at least four perspectives: (1) the GID diagnosis pathologizes normal variation in gender role expression, (2) children with GID are not impaired or inherently distressed, (3) the diagnosis was introduced to the DSM as a veiled attempt to repathologize homosexuality, and (4) GID is a childhood manifestation of homosexuality.

It has been argued that the cross-gender behaviors observed in children with GID are no more than normal, though sometimes extreme, variation in gender role behavior. The GID diagnosis, therefore, pathologizes children who exhibit harmless gender non-conformity and who are simply expressing their interests and inherent tendencies (e.g., Langer & Martin, 2004; Pickstone-Taylor, 2003). Proponents of the GID diagnosis argue that this line of thinking represents biological essentialism and is a simplistic view of a complex phenomenon that is influenced by biological, psychological, and interpersonal processes (Bradley & Zucker, 2003; Zucker, 2006b; Zucker et al., 2012b). Thus, while the critics who argue for a reform of the diagnosis recommend that the criteria should be more stringent to better distinguish gender dysphoric from non-gender dysphoric children with cross-gender behaviors, these critics argue that all children who receive the GID diagnosis are actually displaying nonpathological gender nonconformity.

The GID diagnosis has also been criticized on the grounds that it does not meet the criteria for a mental disorder because children with GID do not show evidence of inherent distress or impairment in functioning (Point D criterion), and, if they do experience distress or socioemotional difficulties, it is simply a reaction to social intolerance of their cross-gender behaviors (e.g., Bartlett et al., 2000; Menvielle, 1998; Wilson et al., 2002). Some argue that the disorder is more a reflection of a gender oppressive society rather than signaling a disorder within the individual (Ault & Brzuzy, 2009). Supporters of the diagnosis have provided compelling reasons to retain GID in the diagnostic nomenclature (Bradley & Zucker, 1998, 2003). For instance, clinic-referred children with GID sometimes verbalize significant unhappiness over their status as males or females and often state the desire to change themselves into the opposite gender (for clinical examples, see Zucker et al., 2012b; Zucker & Bradley,

1995). It is also argued that, even in the absence of explicit statements to be of the opposite sex, pervasive enactments of cross-gender fantasies, such as through role-play and dress-up, is a behavioral manifestation of underlying unhappiness with one's biological sex (Zucker, 2006b).

On a more political level, it has been argued that the inclusion of GID into the DSM was a veiled political maneuver to repathologize homosexuality, which was simultaneously removed from the DSM at the time that GID was introduced (e.g., Ault & Brzuzy, 2009; Sedgwick, 1991). Zucker and Spitzer (2005) noted that the DSM-III included a diagnostic category of ego-dystonic homosexuality; thus, there was no need for a backdoor diagnosis to replace homosexuality. These authors also brought attention to the fact that several clinicians and scientists who recommended the inclusion of GID in the DSM had argued in favor of delisting homosexuality.

The strong association between GID in childhood and homosexuality in adulthood has also added to the controversy surrounding the diagnosis. Follow-up studies of boys with GID have found that the most common outcome in adulthood is desistance of GID with a homosexual sexual orientation (e.g., Green, 1987). Some have interpreted this finding to mean that the cross-gender behaviors observed in children with GID is simply an early manifestation of later homosexuality (e.g., Minter, 1999) and, therefore, should not be pathologized or treated (e.g., Corbett, 1998; Isay, 1997). However, cross-gender behaviors in childhood are not isomorphic with a later homosexual sexual orientation. Some boys with GID grow up to have a later heterosexual sexual orientation (e.g., Green, 1987; Wallien & Cohen-Kettenis, 2008). A second response to this particular criticism is that what constitutes a mental disorder is its operational definition (Green, 2011). Thus, if a child meets diagnostic criteria for a disorder, it is irrelevant to the assignment of a current diagnosis whether the child will meet the diagnosis in the future.

As discussed above, GID is a controversial diagnosis. The diagnosis itself has received much criticism and there remains a significant lack of consensus in the field regarding clinical management of the disorder. Discussions and debates on best treatment practices have raised the issue of the long-term outcomes for boys with GID, particularly in regard to gender identity and sexual orientation (e.g., Zucker, 2008b), a topic now addressed in the present literature review.

1.7 Psychosexual Outcome of Boys with GID

One approach to understanding the developmental trajectory of boys with GID is to retrospectively assess the childhood experiences of adult male-to-female transsexuals. These studies have found that adolescents and adults with GID, particularly those with a co-occurring homosexual sexual orientation (in relation to their birth sex), invariably recall a pattern of childhood cross-gender behavior that corresponds to the DSM criteria for GID (Green, 1974; Smith, van Goozen, Kuiper, & Cohen-Kettenis, 2005; Zucker et al., 2006). However, given the potential problems with retrospective research (for an overview, see Hardt & Rutter, 2004), most notably that the recollections may not be accurate, the ideal methodology to understand the long-term outcome of boys with GID is to identify a group of such children and follow them prospectively. Since the 1960s, a number of such studies have been conducted. Of these, Green's (1987) study and Wallien and Cohen-Kettenis' (2008) study constitute the two most comprehensive long-term follow-up of boys with GID. In addition, the results of 6 other follow-up studies which utilized much smaller sample sizes are also summarized. For clarity, the results on gender identity outcome are presented first followed by the results on sexual orientation outcome. Across all studies, sexual orientation is classified in relation to birth sex.

1.7.1 Gender Identity Outcome of Children with GID

Zucker and Bradley (1995) summarized data from six published follow-up studies of

boys who displayed marked cross-gender behavior (Bakwin, 1968; Davenport, 1986; Kosky, 1987; Lebovitz, 1972; Money & Russo, 1979; Zuger, 1978). The results of these studies are presented as a group due to the small sample size of each study. Across these six studies, a total of 55 boys were seen at follow-up (range, 16-36 years). Of these, 5 (9.1%) were classified as transsexual at follow-up (i.e., they showed persistent gender dysphoria). All 5 persisters had a homosexual sexual orientation.

One of the earliest prospective follow-up studies to utilize a reasonably large sample size was conducted by Green (1987). Green's sample consisted of 66 behaviorally "feminine"³ boys and 56 control boys⁴ who were unselected for their gender identity. Both groups of boys were initially assessed at a mean age of 7 years (range, 4-12 years) and were recruited through various forms of advertisement. Although Green did not utilize a formal DSM diagnosis,⁵ from his clinical descriptions it appears that most of the behaviorally feminine boys would have met criteria for GID. Most of the feminine boys stated their wish to be girls or to grow up to be women, avoided male-typical activities (e.g., rough-and-tumble play, sports), preferred female roles in pretend play, and showed a preference for girls' clothes, toys, and peers (Green, 1974, 1976). Forty-four feminine boys and 35 control boys were available for follow-up assessment in adolescence and adulthood (M age, 18.9 years; range, 14-24). Only a minority of the feminine boys ($n = 12$) received formal therapy between the childhood assessment and the follow-up interview. At follow-up, only one (2.3%) of the 44 behaviorally feminine boys continued to experience gender dysphoria and desired sex reassignment surgery. None of the control boys reported any gender dysphoria.

³ "Feminine" is stated here with quotations to reflect the name Green (1987) assigned to this group of boys.

⁴ The comparison group was matched on a number of variables, including age, number, age, and sex of siblings, marital status of parents, and education level of parents (Green, 1987).

⁵ GID as a diagnostic category had not yet been introduced to the DSM at the time when Green (1987) began data collection.

More recently, Wallien and Cohen-Kettenis (2008) conducted the largest follow-up study to date on boys and girls with GID (77 children; 59 boys, 18 girls). The childhood data were collected as part of the standard assessment of children seen in their specialized gender identity clinic in The Netherlands. At follow-up, 54 participants (40 boys, 14 girls) were successfully traced and completed the follow-up assessment. The remaining 23 participants (19 boys, 4 girls) could not be traced. However, Wallien and Cohen-Kettenis assumed that these untraced participants were desisters on the premise that had they been persisters they would have likely had contact with the clinic and, therefore, included them in the calculation of a persistence rate. Of the 77 children followed prospectively, Wallien and Cohen-Kettenis reported that 21 (12 boys, 9 girls) were still gender dysphoric at follow-up, which yielded a persistence rate of 27% for the total sample of boys and girls with GID. However, when calculated based only on those participants who were actively involved in the follow-up assessment (i.e., excluding the 23 participants who could not be traced at follow-up), the persistence rate was 38.8%.⁶

For comparative purposes, I provide additional details for the boys in Wallien and Cohen-Kettenis' study. The mean age for all 59 boys was 8.3 years (range, 5-12 years) at the initial assessment and 19.4 years (range, 16-28 years) at follow-up. Unfortunately, separate demographic data were not available on the subgroup of boys who were successfully contacted at follow-up. When calculated using only the 40 boys who were successfully traced at follow-up, the rate of persistent gender dysphoria was 30% (12 persisters, 28 desisters). If, however, one used Wallien and Cohen-Kettenis' more liberal calculation of persistence by also including the 19 boys who could not be traced and classifying them as desisters, the persistence rate for boys

⁶ This recalculation was done by me for the purpose of this chapter.

was 20.3%.⁷ All of the persisters met complete diagnostic criteria for GID at follow-up, were treated with puberty suppressing hormonal treatment before the age of 16, and with cross-sex hormones after the age of 16 years.

The rates of GID persistence found by Wallien and Cohen-Kettenis (2008), regardless of whether one uses the liberal or conservative calculation, were considerably higher than that reported by Green (1987) (in fact, more than 8 times as high) and approximately 2-3 times as high as the rate found by Zucker and Bradley (1995) in their review of six studies.⁸

Wallien and Cohen-Kettenis' sample size was large enough to allow for group comparisons to identify potential differences in childhood between the boys who persisted in their gender dysphoria from those who desisted.⁹ There was a significant difference between the persisters and desisters on the diagnosis received in childhood. All of the boys who showed persistent gender dysphoria had met the full criteria for GID in childhood. However, of the 28 (traced) boys who desisted, 17 met full criteria for GID while the remaining 11 were subthreshold. Of the 19 boys who could not be traced at follow-up, 15 met full criteria for GID and 4 were subthreshold. The persisters were also more extreme in their childhood cross-gender behaviors and identification on two dimensional measures, both of which were also used in the present study: (1) the Gender Identity Interview for Children (Wallien et al., 2009; Zucker et al., 1993), a child-report measure, and (2) the Gender Identity Questionnaire for Children (Johnson

⁷ This recalculation of persistence rates for boys only was done by me for the purpose of this chapter and to allow for comparison to the persistence rates for boys with GID obtained in the present study and by Green (1987). These rates were not explicitly reported by Wallien and Cohen-Kettenis (2008).

⁸ Drummond et al. (2008) reported on the long-term outcome of 25 biological females with GID assessed in childhood (mean age, 8.88 years) at the Child and Adolescent Gender Identity Service at CAMH. Drummond et al. reported a persistence rate of 12%; 3 of the 25 girls were gender dysphoric at follow-up (mean age, 23.24).

⁹ Wallien and Cohen-Kettenis (2008) compared their outcomes groups on childhood measures of sex-typed behavior, but not on childhood demographic variables or childhood behavioral problems. Group comparison on childhood GID diagnosis was done using chi-square analyses. Group comparison on the Gender Identity Interview and Gender Identity Questionnaire for Children were done using *t*-tests.

et al., 2004), a parent-report measure.¹⁰ These data indicated that boys with more extreme cross-gender identification in childhood were more likely to be persisters than desisters.

1.7.1.1 Methodological Issues

Two methodological issues regarding the follow-up studies need to be mentioned. First, with the exception of Green's (1987) study, none of the follow-up studies included a clinical control group (i.e., referred for reasons other than gender identity concerns) or community control group. Therefore, interpretation of follow-up data relied on evidence from the literature on adults with GID (Zucker, 1985). Second, during the follow-up assessments, particularly those in which data were obtained through clinical interview (e.g., Green, 1987), participants were asked to discuss an extremely sensitive and personal aspect of their lives—their psychosexual development. Due to the potential effects of social desirability on participants' responses, it is possible that the rates of persistent gender dysphoria (and also homosexual outcomes) in these studies were an underestimate. It is unlikely that participants would have reported a homosexual or GID outcome if, in fact, they were not homosexual or experiencing gender dysphoria; thus, an overestimation was unlikely to have occurred. Unfortunately, social desirability was not measured by Green or Wallien and Cohen-Kettenis; thus, the effects of this phenomenon on their respective results are unknown.

1.7.1.2 Process of GID Desistence

There have been no quantitative follow-up studies that have systematically examined the developmental process through which GID desists (e.g., how and at what age). Some authors suggest that desistence typically occurs sometime around puberty or early adolescence (de Vries & Cohen-Kettenis, 2012; Wallien & Cohen-Kettenis, 2008). However, one should be skeptical in

¹⁰ The Gender Identity Interview and Gender Identity Questionnaire for Children were developed in the Gender Identity Service at the Centre for Addiction and Mental Health in Toronto.

viewing puberty as *the* transformative period in the lives of children with GID with regard to their gender identity. Some gender-referred children show changes in their gender identity before puberty and, in fact, desist in their dysphoria during childhood (for case examples, see Zucker, 2006c; Zucker & Bradley, 1995).

The results of a recent qualitative study by Steensma et al. (2011) suggested that desistence may occur between the ages of 10-13 years and is likely influenced by psychosocial and psychosexual factors. In this study, 25 adolescents (13 boys, 12 girls; M age, 15.88 years; range, 14-18) who had been seen in a specialized gender identity clinic in The Netherlands in childhood and diagnosed with GID were contacted in adolescence for a follow-up interview. During the follow-up interview, participants were asked to discuss their childhood gender role behaviors, stability of gender identity, sexual orientation, and physical development. Thus, the data on childhood gender-role behavior and change in gender identity between the initial assessment and follow-up were based on retrospective recall. The primary goal of the study was to obtain qualitative data on the developmental course of GID, including factors that contributed to GID persistence and desistence. Of the 13 biological males in this study, 7 had applied for sex reassignment surgery and can, therefore, be considered persisters. The remaining 6 were desisters. One should not, however, extract a persistence rate from these data because this was not the goal of this study. Second, persistence and desistence were not clearly operationalized. Third, as this was a qualitative study, there was no quantitative comparison between the participants and non-participants and differences between the groups could have affected gender identity outcome. Thus, given that the participants might have represented a biased sample, caution should be exercised in drawing conclusions about the obtained persistence rate.

Several findings from this study warrant mention. First, both persisters and desisters recalled that around the age of 6 or 7 years they started to identify with and expressed a wish to be of the opposite sex, though they had exhibited cross-gender behavior prior to this. The underlying “motives” for childhood cross-gender identification appeared to be different for the persisters and desisters. The persisters recalled having felt as though they were the opposite sex. In contrast, the desisters recalled having wished they were of the opposite sex but did not feel they were the opposite sex. Second, the period from age 10 to 13 years of age appeared to be significant in the developmental trajectory for both persisters and desisters. Both groups of adolescents reported that three factors affected their feelings of gender dysphoria and either lessened or intensified it: their social environment (e.g., peer relations), anticipation about and experience of puberty, and emerging sexual attraction. This study highlighted the need for studies to prospectively follow children with GID beyond adolescence and into adulthood while periodically monitoring stability and change in their psychosexual development, particularly during the transition from childhood to adolescence. For example, one of the males in the desister group continued to experience some feelings of gender dysphoria but was not interested in living as woman. As the authors noted, a longer follow-up period may help to clarify whether this participant was experiencing protracted gender dysphoria that would eventually diminish or whether some form of mild gender dysphoria would remain a stable aspect of his psychological functioning.

The results of Steensma et al.’s study can be considered preliminary given the small sample size and retrospective recall of gender experiences from assessment to follow-up. This study also represents the first attempt in the literature to account for the process through which GID persists or desists. Future studies utilizing a prospective systematic design (i.e., regular

follow-up intervals following the childhood assessment) with quantitative measurements of relevant variables are needed. Further, there are other factors beyond those examined by Steensma et al. that may potentially contribute to the developmental course of GID (e.g., psychiatric functioning, psychotherapy) and that would require empirical investigation.

1.7.2 Gender Identity Outcome of Adolescents with GID

Clinical observation and empirical evidence suggest that persistence of gender dysphoria, including the desire for sex change, is higher among patients assessed for the first time during adolescence and then followed up than among patients first assessed in childhood and then followed prospectively (Zucker & Bradley, 1995).

Cohen-Kettenis and van Goozen (1997) reported follow-up data on 33 adolescents with GID seen at a specialized gender identity clinic in The Netherlands. Of the 33 adolescents (M age at initial assessment, 17.5 years; range, 15-20), 22 (66.6%) went on to receive cross-sex hormonal therapy and some form of sex reassignment surgery. Of the remaining 11 adolescents, 8 were not diagnosed with “transsexualism” (presumably, they did not meet criteria for GID) and were, therefore, not recommended for sex reassignment surgery. The remaining 3 participants were diagnosed with transsexualism but, for a variety of reasons, including severe comorbid psychopathology, were not recommended for any cross-sex hormonal treatment. The “true” persistence rate of these adolescents could be higher than 66.6% because there were no data on whether any of the 11 participants who did not initially receive cross-sex hormonal or surgical interventions did so at a later date. This persistence rate of 66.6% is much higher than the persistence rates found in follow-up studies of boys who are first referred in childhood.

Zucker et al. (2011) reported on 109 adolescents who were assessed in the Gender Identity Service at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada. Of

the total sample, 66 (60.6%) were recommended for puberty blocking hormonal therapy and 43 (39.4%) were not. The percentage of adolescents referred for hormonal therapy was similar to the 66.6% reported by Cohen-Kettenis and van Goozen (1997). It should be noted that the Zucker et al. study was geared towards examining which factors (e.g., demographic, psychosexual) influenced the clinical decision to recommend or not recommend puberty blocking hormones. Blockers were more likely to be recommended for those adolescents who were more extreme in their current gender dysphoria and childhood cross-gender behavior. Thus, while follow-up data were available for some participants, this study was not a systematic follow-up study per se. It would be informative to know whether the participants who did not receive blockers persisted or desisted in their gender dysphoria.

*1.7.3 Sexual Orientation Outcome*¹¹

In their review of six follow-up studies of boys with GID (Bakwin, 1968; Davenport, 1986; Kosky, 1987; Lebovitz, 1972; Money & Russo, 1979; Zuger, 1978), Zucker and Bradley (1995) also summarized data on sexual orientation outcome. Of the 55 boys reported on in these studies, 13 were classified as “Uncertain” with regard to sexual orientation, in part, because they were not sexually active and data regarding sexual orientation in fantasy were not definitive. Of the remaining 42 cases, 26 (61.9%) were classified as homosexual (this includes the 5 individuals who were persisters with a homosexual sexual orientation) and 16 (38.1%) were classified as heterosexual. In these six follow-up studies, it is unclear if sexual orientation was classified according to fantasy or behavior.

In Green’s (1987) study, sexual orientation in fantasy and behavior was assessed using a semi-structured interview and rated using Kinsey’s 7-point scale where 0 = exclusively heterosexual and 6 = exclusively homosexual (Kinsey et al., 1948). Of the 44 feminine boys

¹¹ Across all studies, sexual orientation is classified in relation to birth sex.

assessed at follow-up, 33 (75%) were classified as bisexual/homosexual in fantasy (Kinsey ratings of 2-6) and 11 (25%) were classified heterosexual in fantasy (Kinsey ratings of 0-1). Of note, the persister in Green's study reported a homosexual sexual orientation, in both fantasy and behavior. Unlike the feminine boys, all of the clinical control boys were classified as heterosexual in fantasy. At follow-up, only 30 of the feminine boys reported having had sexual experience. Of these, 24 (80%) were classified as bisexual/homosexual in their sexual behavior and the remaining 6 (20%) were classified as heterosexual in behavior. In the control group, 25 of the 35 boys reported sexual experiences at follow-up. Of these, 1 (4.0%) was classified as non-heterosexual (he reported bisexual sexual experiences) and the others were classified as heterosexual. Therefore, depending on whether sexual orientation was classified according to fantasy or behavior, 75-80% of the 44 feminine boys were classified as bisexual/homosexual in their sexual orientation compared to only 0-4% of the control boys.

In Wallien and Cohen-Kettenis' (2008) study, sexual orientation was assessed using the 9-item Sexual Orientation Questionnaire (SOQ) (<http://links.lww.com/A569>). Items on the SOQ pertained to four domains of sexual orientation: sexual behavior (4 items), sexual fantasy (2 items), sexual attraction (2 items), and sexual identity (1 item). Response options for questions pertaining to sexual behavior and fantasy reflected Kinsey's 7-point scale. Although this study included biological males and females, only data for males are presented here. Of the 40 males who were contacted for follow-up, data on sexual orientation in fantasy were only available for 21. Of these, 17 (81%) were classified as bisexual/homosexual and 4 (19%) as heterosexual. Data on sexual orientation in behavior were available for 19 males (13 desisters, 6 persisters). Of these, 15 (79%) were classified as bisexual/homosexual and 4 (21%) were classified as

heterosexual. When sexual orientation was examined according to gender identity outcome,¹² 10 (77%) and 13 (81%) of the desisters were classified as bisexual/homosexual in behavior and fantasy, respectively. The remaining desisters were classified as heterosexual, (3) 23% in behavior and (3) 19% in fantasy. For the 6 persisters on which requisite data were available, 5 (83%) were classified as bisexual/homosexual in both fantasy and behavior and 1 (17%) was classified as heterosexual in fantasy and behavior.

In the studies by Green (1987) and Wallien and Cohen-Kettenis (2008), most boys with GID later developed a bisexual/homosexual sexual orientation, with rates that ranged from 75-81%. These rates are substantially higher than the currently accepted base rate of a homosexual sexual orientation in males of 3.1% (Laumann, Gagnon, Michael, & Michaels, 1994).

That some males with GID develop a heterosexual sexual orientation in adulthood is not fully understood. It has been suggested that perhaps the degree of cross-gender identification may affect sexual orientation outcome (Zucker, 1985). On the latter point, Wallien and Cohen-Kettenis (2008) found a significant difference between their sexual orientation groups on a parent-report measure of childhood sex-typed behavior (the Gender Identity Questionnaire for Children). However, when these analyses were redone for the desisters only, the difference was no longer significant and suggested that the extreme cross-gender scores of the persisters was responsible for the overall group difference on this measure.

Green (1987) also examined the relationship between degree of cross-gender behavior in childhood and sexual orientation at follow-up. For all participants, Green (1987) computed a childhood composite “extent of femininity” score on the basis of six behaviors: cross-dressing, rough-and-tumble play, wish to be a girl, desire to be like father, attention to mother’s fashion,

¹² For the desisters, data on sexual orientation in fantasy and behavior were available for only 16 and 13 participants, respectively. For persisters, data on sexual orientation in fantasy and behavior were available for only 5 and 6 participants, respectively. Wallien and Cohen-Kettenis (2008) did not explain these missing data.

and female-type doll-play. Across the entire sample, there was a significant correlation between “extent of femininity” and sexual orientation; however, within the “feminine” group only, this association was not significant for sexual orientation in fantasy or behavior. Green (1987) concluded that the lack of “range” (i.e., variability) in “extent of femininity” and sexual orientation contributed to the insignificant finding.

Green also examined whether there were specific childhood features that distinguished which “feminine” boys developed a homosexual sexual orientation from those who developed a heterosexual sexual orientation. Of 14 variables of childhood sex-typed behavior, three variables were related to sexual orientation at follow-up: female role-play, doll-play, and female peers. With age at childhood assessment controlled for, preference for female peers and doll play were significantly correlated with sexual orientation in fantasy, but not behavior. Female role play was, however, significantly correlated with both fantasy and behavior (Green, Roberts, William, Goodman, & Mixon, 1987).

One criticism of these prospective studies is that they followed up children who showed extreme forms of cross-sex behavior and identification, most of whom were clinically referred. As such, the generalizability of these studies is limited to similar groups of children. In the context of this limitation, Steensma et al. (2012) conducted a 24-year prospective study of 879 (406 boys, 473 girls) non-clinically referred children, unselected for their gender identity, who were part of a population-based study (for a description of the study, see section on Prevalence of GID). At follow-up, sexual orientation was assessed by asking four questions, each of which pertained to a different domain of sexual orientation: sexual attraction (“To whom do you feel attracted?”), sexual fantasy (“About whom do you fantasize sexually?”), sexual behavior (“With whom do you have sexual contact?”), and sexual identity (“How do you identify yourself?”). For

sexual attraction, fantasy, and behavior, participants' responses were coded using Kinsey's 7-point scale. At follow-up, 11 (2.7%) of the 406 boys were bisexual/homosexual in fantasy and 10 (2.5%) were bisexual/homosexual in behavior. Steensma et al. also examined sexual orientation outcome separately for the gender-variant (10 males, 41 females) and non-gender variant (396 males, 432 females) groups. Of the 10 gender variant boys, 2 (20%) were bisexual/homosexual in fantasy and behavior and the remaining 8 (80%) were heterosexual in fantasy and behavior. Of the 396 non-gender variant boys, 9 (2.3%) and 8 (2.1%) were bisexual/homosexual in fantasy and behavior, respectively. I used Fisher's exact test to determine if these represented significant differences in sexual orientation across the two subgroups of boys (i.e., gender variant versus non gender-variant). For both fantasy and behavior, there was a significant difference in the number of boys classified as bisexual/homosexual versus heterosexual (both $ps < .05$). Depending on whether one looks at fantasy or behavior, the prevalence of bisexuality/homosexuality in the gender variant boys was 8.7-9.5 times higher than the prevalence rate of bisexuality/homosexuality in the non-gender variant boys. Thus, when a sample of boys unselected for their gender identity were followed up into adulthood, those who were at the cross-gendered end of the spectrum were significantly more likely to develop a bisexual/homosexual sexual orientation.

The rates of bisexuality/homosexuality obtained by Steensma et al. for the entire sample of males (2.5-2.7%) were substantially lower than those obtained by Green (1987) and Wallien and Cohen-Kettenis (2008) in their follow-up of boys with gender dysphoria. This difference is not surprising and may be attributable to sample differences; however, an interpretative caution is in order. Steensma et al. measured gender variance in childhood using 2 items on the CBCL; they did not include specific measures of gender identity, gender role, or gender dysphoria. Thus,

the actual extent of cross-gender behaviors in their sample of males is unclear. On the other hand, the males in Green's and Wallien and Cohen-Kettenis' studies were extreme in their cross-gender behaviors on measures of gender identity and gender role. Given that the boys in Steensma et al.'s study were taken from the general population and were unselected for their gender identity it is likely, and expected, they would have significantly less cross-gender behaviors compared to the boys seen by Green and by Wallien and Cohen-Kettenis. Indeed, the rate of bisexuality/homosexuality obtained by Steensma et al. is similar to the base rate of a homosexual sexual orientation in males of 3.1% (Laumann, Gagnon, Michael, & Michaels, 1994). At the same time, and consistent with Green's (1987) study, which included a control group, the gender variant boys in Steensma et al.'s study were more likely to develop a bisexual/homosexual sexual orientation compared to the non-gender variant boys. Similar to the developmental course of GID, these results suggest that there may also be a dosage effect on sexual orientation outcome—the more gender variance in childhood, the higher the likelihood of homosexuality.

1.7.4 Gender Identity and Sexual Orientation Outcomes in Boys with GID: Summary

The prospective follow-up studies of boys with GID (or pervasive cross-gender behavior in the case of studies conducted prior to 1980) suggests that there are four outcomes: (1) persistence of GID, with a co-occurring bisexual or homosexual sexual orientation, (2) persistence of GID, with a co-occurring heterosexual sexual orientation, (3) desistance of GID, with a co-occurring homosexual sexual orientation, and (4) desistance of GID, with a co-occurring heterosexual sexual orientation. Of these, a desistance of GID with a co-occurring homosexual sexual orientation appears to be the most common (e.g., Green, 1987; Wallien & Cohen-Kettenis, 2008).

1.8 Retrospective Studies of Homosexual Men: Summary of Key Findings

As the current study utilized a longitudinal follow-up design, the results of retrospective studies are only briefly summarized to highlight the key findings and to inform the extent to which prospective and retrospective results converge. In the 1960s, 1970s, and 1980s, studies were conducted which identified significant differences between heterosexual and homosexual adults on their recollections of childhood sex-typed behaviors (e.g., Whitam, 1977). However, some authors were skeptical about these findings. Carrier (1986), for example, felt these results were obtained using skewed samples and, therefore, could not be generalized to all homosexual men and women. Following the publication of a meta-analysis by Bailey and Zucker (1995), the strong relationship between childhood sex-typed behavior and sexual orientation was more or less confirmed.

Bailey and Zucker reviewed 41 studies, 32 of which compared the recalled childhood (≤ 12 years of age) sex-typed behaviors of heterosexual and homosexual men. Bailey and Zucker found that, on average, homosexual men recalled substantially more cross-gendered behavior during childhood than heterosexual men. The effect sizes were large (Cohen's $d = 1.31$) (Cohen, 1988) and "were among the largest effect sizes ever reported in the realm of sex-dimorphic behaviors." The heterosexual and homosexual adults differed on various domains of childhood sex-typed behavior, including rough-and-tumble play, toy and activity preferences, role playing, cross-dressing, and preferred sex of peers. Several studies conducted after the Bailey and Zucker (1995) meta-analysis yielded similar results (e.g., Bailey & Oberschneider, 1997; Bogaert, 2003; Cohen, 2002; Zucker et al., 2006; for a review, see Zucker, 2008c).

Similar results have also been found in retrospective studies of non-Western cultures, including Samoa (Bartlett & Vasey, 2006), Turkey, and Thailand (Cardoso, 2009). As one

example, Bartlett and Vasey conducted a retrospective study of childhood sex-typed behavior in the Samoan *fa'afafine*, Samoan men, and Samoan women. *Fa'afafine* are biological males who manifest gender atypical behavior. In Samoa, the *fa'afafine* are essentially a third gender group and, for the most part, self-identify as such. Some adult *fa'afafine* present socially as females through clothing choice, hair, voice, and mannerisms, while others adopt only some aspects of female gender roles. Most *fa'afafine* are androphilic, meaning they are sexually attracted to biological males. The *fa'afafine* recalled engaging in significantly more female-typical (e.g., playing with girls' toys, putting on make-up) and less-male typical behaviors (e.g., playing with boys, playing rough sports) in childhood compared to men. Further, their recollections of childhood sex-typed behaviors did not differ significantly from those of Samoan women. Some *fa'afafine* also recalled an aversion towards male-typical activities.

Despite the consistency of retrospective studies, some authors continue to challenge that a relationship exists between childhood sex-typed behavior and adult sexual orientation, partly on the premise that retrospective recall of childhood behavior may be distorted (e.g., Gottschalk, 2003). A number of studies have utilized methodology that minimizes the chance of a recall bias and the results speak against the retrospective distortion hypothesis. In one study, researchers examined childhood gender nonconformity in homosexual and heterosexual adults by examining videos from their childhood (1-15 years of age) as a visual recording will not be susceptible to memory bias (Rieger, Linsenmeier, Gygax, & Bailey, 2008). The adults who self-labeled as homosexual were judged (by raters masked to their sexual identity) to be significantly more gender nonconforming as children than the adults who self-labeled as heterosexual. In another line of research that utilized heterosexual and homosexual participants, there was a significant correlation between the retrospective recall of childhood sex-typed behavior by the participants

and ratings of the participants by his or her mother (Bailey, Miller, & Willerman, 1993; Bailey, Nothnagel, & Wolfe, 1995; Bailey, Willerman, & Parks, 1991).

In sum, the prospective data on sexual orientation outcome of boys with GID converge decently with retrospective studies of homosexual adults. Owing to these two lines of evidence, it is now generally accepted that childhood gender role behavior is not only strongly related to sexual orientation in adulthood in clinical and non-clinical samples but that it can also predict sexual orientation outcome (for a review, see Bailey & Zucker, 1995; Zucker, 2008c). There are, however, a few caveats to keep in mind. Some boys with GID followed prospectively into adolescence and adulthood have a heterosexual sexual orientation (e.g., Cohen-Kettenis & Wallien, 2008; Green, 1987). Studies that systematically examined childhood correlates of sexual orientation differentiation are needed to help us better understand this variability in outcome. As well, a proportion of homosexual men do not recall a childhood history of cross-gender behavior (Bailey & Zucker, 1995). Of the homosexual men who recall a cross-gendered childhood, it is unclear how many of these individuals would have met the full diagnostic criteria for GID as children.

1.9 Childhood Sex-Typed Behavior and Sexual Orientation: Explaining the Linkage

Both biological and psychosocial explanations have been offered to explain the linkage between childhood sex-typed behavior and sexual orientation (for reviews, see Green, 2008; LeVay, 2011; Zucker, 2008c).

1.9.1 Biological Explanation: Influence of Genes

One biological explanation is that childhood cross-gendered behaviors and adult sexual orientation are strongly linked because they are both components of psychosexual differentiation that develop under the influence of genes. A number of studies have found that homosexuality is

highly familial—gay men have more gay siblings than do straight men (e.g., Bailey et al., 1999; Bailey & Bell, 1993; Bailey, Dunne, & Martin, 2000; Bailey, Willerman, & Parks, 1991; Hershberger, 1997; Pillard, Poumadere & Carretta, 1982; Pillard & Weinrich, 1986; Schwartz, Kim, Kolundzija, Rieger, & Sanders, 2010). These studies have found that brothers of homosexual men are homosexual 7% to 22% of the time, with a median rate of approximately 10% (for reviews, see Bailey & Pillard, 1995; Mustanski, Chivers, & Bailey, 2002) which is well above the estimated base rate of homosexuality in the general population of biological males (Laumann et al., 1994). Differences across studies in recruitment process, assessment of sexual orientation, source of information (e.g., the gay men themselves reporting about their siblings vs. interviewing the siblings of gay men) likely account for the variation in these findings. That homosexuality tends to cluster in families could be attributed to genetic or shared environmental factors. If genes do contribute to sexual orientation, one would also expect a clustering of homosexuality among family members without shared environment (e.g., nonsibling relatives). Indeed, increased rates of homosexuality or bisexuality have been found among uncles and male cousins of gay men (Bailey, Bobrow, Wolfe, & Mikach, 1995).

Twin studies have supported a genetic interpretation of the familiarity findings described above. One of the earliest twin studies of male homosexuality reported a 100% concordance rate for 37 monozygotic (MZ) twin pairs compared with a 15% rate for 26 dizygotic (DZ) pairs (Kallmann, 1952). This study has since been strongly criticized because subjects were primarily recruited from psychiatric institutions and because the methodology through which zygosity was established was not clearly delineated (Mustanski, Chivers, & Bailey, 2002). The results of subsequent twin studies suggest that the concordance rates for homosexuality among MZ twins are much lower than 100% and appear to be closer to 50%. In a study of 115 male twin pairs,

Bailey and Pillard (1991) found a concordance rate for homosexuality of 52% among MZ twins compared to 22% among DZ twins. Whitam, Diamond, and Martin (1993) found higher concordance rates: 65% for MZ twins and 29% for DZ twins. One criticism of these studies is that they relied on advertisement; thus, there may have been a self-referral bias such that gay individuals with a gay twin might have been more likely to respond to the study advertisement compared to gay individuals without a gay twin and this could have resulted in an inflation of concordance rates (Bailey, Dunne, & Martin, 2000; LeVay, 2011). More recent studies have examined concordance rates for homosexuality among pairs of twin from large registries that were created without reference to the twins' sexual orientation and these have reported lower concordance rates compared to self-selected samples. In a study of Australian twins, for example, Bailey, Dunne, and Martin (2000) found a concordance rate of 20% among male MZ twins.

The findings from behavior genetics studies also support a genetic basis for homosexuality. In a reanalysis of the Australian twin data (Bailey, Dunne, & Martin, 2000), Kirk, Bailey, Dunne, and Martin (2000) estimated the heritability of homosexuality in males to be approximately 30%. In other words, genetic influences accounted for 30% of the variation of sexual orientation in men. In a more recent population based study of Swedish twins, the heritability of homosexuality in males ranged from 34%-39% (Långström, Rahman, Carlström, and Lichtenstein, 2010).

The strong relationship between cross-gender behavior in childhood and adult homosexuality combined with twin studies demonstrating a genetic basis for homosexuality raises at least two questions: (1) Is there a genetic basis for cross-gender behavior?; and (2) Is there a common genetic basis for both cross-gender behavior and sexual orientation? Bailey,

Dunne, and Martin (2000) also measured childhood gender nonconformity of the twins in their study and found that heritability accounted for 50% of variance in recalled childhood gender nonconformity among men. Monozygotic twins who are both gay were more similar in their cross-gender behavior (correlation of gender nonconformity = .54) compared to dizygotic twins who are both gay (correlation of gender nonconformity = .14). Similar results were obtained by Alonko et al. (2010) in a study of Finnish twins taken from a national register: monozygotic (male) twins had higher correlations on both gender atypical behavior and sexual orientation ($r = .56$ and $.50$, respectively) compared to dizygotic twins ($r = .27$ and $.25$, respectively). These findings suggested that childhood gender nonconformity, like homosexuality, is heritable. In fact, a study of Dutch children taken from a national twin register, and who were therefore unselected for gender identity or sexual orientation, estimated that 70% of the variance in cross-gender behavior was accounted for by genetic factors (van Beijsterveldt, Huzdiak, & Boomsma, 2006). Alonko et al. (2010) found a large genetic correlation ($r = .73$) between gender atypical behavior and sexual orientation for the male twin pairs, which suggests that a shared set of genes is partially responsible for both childhood gender nonconformity and adult homosexuality.

1.9.2 Biological Explanation: Role of Prenatal Hormones

Another prominent biological explanation for the linkage between childhood sex-typed behavior and sexual orientation is that they are both influenced by common biological processes involving prenatal hormones. Research on biological females with congenital adrenal hyperplasia (CAH) provides evidence for the influence of prenatal hormones on sex-typed behaviors. In CAH, a defect in the enzyme involved in cortisol production results in the adrenal glands producing higher than normal levels of androgens. As the condition is recognized at birth and corrected, the period of abnormal androgen exposure is generally limited to the prenatal

period. Data from several groups of researchers consistently show that girls with CAH show a male-typical pattern of toy and activity preferences from childhood through adulthood (for reviews, see Hines, 2002, 2010, 2011). For example, they are, on average, more active and aggressive than girls without CAH (e.g., Pasterski et al., 2007) and have toy preferences similar to those of boy (e.g, Berenbaum & Hines, 1992; Berenbaum & Snyder, 1995; Pasterski et al., 2005, 2011; Servin, Nordenström, Larsson, & Bohlin, 2003). Girls with CAH also appear to have an enhanced preference for boys as playmates (e.g., Pasterski et al., 2011; Servin et al., 2003) and engage in more rough-and-tumble play compared to unaffected girls (e.g., Pasterski et al., 2011). The extent of male-typed interests in childhood in females with CAH appears to be correlated with the degree of prenatal androgen exposure (Nordenström, Servin, Bohlin, Larsson, & Wedell, 2002).

In adulthood, women with CAH have a higher rate of bisexuality/homosexuality compared to unaffected women (Hines, Brook & Conway, 2004; Meyer-Bahlburg, Dolezal, Baker, Ehrhardt, & New, 2006; Meyer-Bahlburg, Dolezal, Baker, & New, 2006; Zucker et al., 1996). Women with CAH also report unhappiness with their female gender role and gender identity (e.g., Hines et al., 2004). In a review of the literature on women with CAH (total $n = 250$)¹³, Dessens, Slijper, & Drop (2005) estimated that approximately 5% experienced gender dysphoria and 1.6% pursued a gender transition (see also for a review, Hines, 2010). These percentages are significantly higher than the estimated prevalence rate of FtM transsexualism in the general population of biological females (1:30,400) (Bakker, van Kestern, Gooren, & Bezemer, 1993). Based on their review, women with CAH were approximately 500 times more likely than women in the general population to experience severe gender dysphoria and transition to the male gender role. It has been argued that the excessive androgen exposure in women with

¹³ Included studies and case reports.

CAH is the linkage factor that explains the behavioral masculinity in childhood and gender dysphoria and bisexuality/homosexuality in adulthood (Zucker, 2008c).

Most boys and adults with GID have normally developed genitalia (Green, 1976). Thus, if prenatal androgen levels are implicated in the etiology of GID, the effects are such that genital development is not affected in any obvious way. Animal studies have shown that there are different sensitive periods for prenatal androgen effects on behavior and genital anatomy. For example, in female rhesus macaques, Goy, Bercovitch, and McBair (1988) were able to induce behavioral masculinization without accompanying genital ambiguity (i.e., the genitals were not masculinized) by altering the timing of prenatal androgen exposure. These results suggest that, depending on the timing of prenatal exposure to androgens, there may be subsequent effects on behavior, anatomy or both.

1.9.3 Psychosocial Explanations

Psychosocial theories have also been offered in explanation for the association between childhood sex-typed behavior and adult sexual orientation. Green (1987) theorized that, in childhood, pre-homosexual boys identify with their mothers and lack a close relationship with their fathers and other boys, which results in “male affect starvation.” In adolescence, homoerotic contact is used in some compensatory manner to achieve closeness with other males. It is unclear how this formulation would account for males who do not have a close relationship with their father or other adult males but grow up to be heterosexual. In Bem’s (1996, 2008) “exotic becomes erotic” theory of sexual orientation, biological factors influences a child’s temperament which, in turn, influences a child’s preference for same-sex versus opposite-sex peers. Children feel similar to the peers with whom they socialize and different from those with whom they do not socialize. This feeling of being different results in physiological arousal,

which is then transformed to sexual arousal. For example, effeminate boys who prefer female peers initially feel different from boys and experience them as “exotic.” Later in development, these exotic feelings become erotic feelings. It is unclear how Bem’s theory would account for homosexual adults who were stereotypically masculine in childhood.

1.10 Associated Psychopathology in GID

One goal of the present study is to identify whether there are within-group childhood characteristics, including childhood behavior problems, that were predictive of long-term outcomes of boys with GID. Thus, the remainder of this chapter will focus on associated psychopathology in GID and will conclude with a conceptual framework for and goals of the present study.

1.10.1 Children with GID

1.10.1.1 Behavior Problems in Children with GID

Studies on associated psychopathology in children with GID have taken two general approaches. One approach is to examine the presence of general psychopathology or behavior problems as would be reported on such measures as the CBCL. A second approach has been to examine the presence of other DSM diagnoses in children with GID.

Information on associated psychopathology or general behavior problems in children with GID has been systematically obtained from parent-report data on the CBCL. Using maternal-report data, Zucker and Bradley (1995) compared 161 gender-referred boys and 90 siblings on five indices of disturbance: the number of elevated narrow-band scales ($T > 70$), number and sum of items rated 1 or 2, and T scores for the Internalizing and Externalizing broad-band scales. On all five indices, gender-referred boys had significantly higher levels of behavioral disturbance compared to their siblings. Further, the boys with GID had significantly

higher Internalizing *T* scores than Externalizing *T* scores; however, there was no significant difference between these scores for their siblings. Zucker and Bradley also compared 46 gender-referred boys pair-matched¹⁴ to 46 clinical control boys on the five CBCL indices described above: there was no significant difference between the groups on any of the indices. Cohen-Kettenis et al. (2003) found similar rates of behavior problems in a cross-national, cross-clinic comparison of 358 gender-referred children assessed at the CAMH in Toronto and 130 gender-referred children assessed in The Netherlands. In this study, boys with GID also showed more internalizing than externalizing problems on the CBCL.

CBCL studies of gender-referred children have found two other noteworthy patterns. First, there appears to be a relationship between age and degree of behavior problems, with older children having more behavior problems than younger children (Cohen-Kettenis et al., 2003; Zucker & Bradley, 1995). For example, in the Cohen-Kettenis et al. study, 26.1% of 3- to 5-year-old children in the Toronto sample had a CBCL sum score that was in the clinical range (>90th percentile) compared to 62.1% of 6- to 12-year-old children. The corresponding percentages for the Dutch sample were 43.8% and 61.7%, respectively.

Second, children with GID appear to have more peer relationship difficulties compared to their siblings (Zucker, Bradley, & Sanikhani, 1997). Further, gender-referred boys seem to have poorer peer relationships and experience more negative social consequences for their cross-gender behavior compared to gender-referred girls (Cohen-Kettenis et al., 2003; Wallien, Veenstra, Kreukels, & Cohen-Kettenis, 2010). Cohen-Kettenis et al. also found that poor peer relations in boys with GID was a significant predictor of CBCL behavior problems and accounted for 32% of the variance. Thus, poor peer relations may mediate the relationship between cross-gender behavior and psychopathology.

¹⁴ Pairs were matched as closely as possible to age, IQ, parents' social class, and parents' marital status.

These findings are not surprising. Even among children unselected for their gender identity, there is evidence that gender nonconforming behavior is associated with overall adjustment problems (Carver et al., 2003; Rieger & Savin-Williams, 2012; Yunger et al., 2004). Studies of children unselected for their gender identity have also demonstrated that children tend to react negatively to gender-atypical peers and may resist developing friendships with these children (Fagot, 1977; Martin, 1989) and effeminate boys, in particular, receive more negative feedback from peers than masculine girls about their cross-gender behavior (Blakemore, 2003; Fagot, 1977). In an observational study of playmate preferences, non-referred boys were more likely to choose another non-referred boy as a favourite playmate than to choose a boy with GID (Fridell, 2001). On the other hand, a recent study showed that gender referred children are accepted by peers of the opposite sex and have better relations with opposite-sex than same-sex peers (Wallien et al., 2010). Thus, while gender-referred boys may be accepted by female peers, there is likely still a significant amount of ostracism experienced from same-sex peers. Zucker (2005c) conjectured that peer ostracism may also contribute to the above noted relationship between age and behavior problems in children with GID as older children with marked cross-gender behavior may experience relatively more social ostracism compared to younger children who engage in similar behaviors (see Zucker, Wilson-Smith, Kurita, & Stern, 1995).

In recent years, a new line of clinical research has suggested that some children with GID may have comorbid Pervasive Developmental Disorder (PDD), particularly Asperger's Disorder (e.g., de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010; Landén & Rasmussen, 1997; Mikkades, 2002; Zucker et al., 2012b). One explanation for a possible linkage between these two relatively rare disorders is the intense focus/obsessional interest in specific activities (e.g., Klin, Danovitch, Merz, & Volkmar, 2007). Postema et al. (2011) examined two

items on the CBCL which measure obsessions (Item 9: “Can’t get his/her mind over certain thoughts; obsession”) and compulsions (Item 66: “Repeats certain acts over and over; compulsions”) in 528 gender referred children (435 boys, 93 girls) and 414 siblings (239 boys, 175 girls). Items are scored based on the past 6 months on a 0-2 scale where 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. For Item 9, 61.5% of gender-referred boys received a score of 1 or 2, compared to 27.3% of their male siblings, and 49% of referred boys in the CBCL standardization sample (Achenbach, 1991). For Item 66, 26.2% of gender referred boys received a score of 1 or 2, compared to 10.5% of their male siblings, and 26% of referred boys in the CBCL standardization sample. For both Items 9 and 66, the comparison between gender-referred boys and their siblings was significant. These preliminary results support the idea that boys with GID (and, generally, children with GID) show an apparent elevation in obsessional interests, which may be one reason for the observed comorbidity of GID and PDD. For the gender-referred boys, gender-related themes constituted more than half (54.6%) of the examples provided by their mothers.

In summary, children with GID display significantly more behavior problems compared to their siblings and non-referred children but typically display as many behavior problems as other clinical populations, with older children with GID having more behavior problems than younger children. Boys with GID typically present with more internalizing than externalizing difficulties, such as separation anxiety. Furthermore, gender-referred children, boys in particular, have poor peer relations and this was postulated to mediate the relationship between cross-gender behavior and behavior problems. The role of peer relations in the lives of children with GID is emphasized by the fact that, for some clinicians, a primary goal of treatment for gender-

referred children is to prevent social ostracism and improve peer relations (Zucker & Bradley, 1995).

1.10.1.2 Comorbidity in Children with GID

Over 25 years ago, Coates and Person (1985) found that, in 25 boys (M age, 7.4 years) who met criteria for GID, 15 (60%) also met criteria for separation anxiety disorder (SAD). Coates and Person did not provide details on how they assessed for the presence of SAD, beyond a general statement that DSM-III criteria were used nor did they provide data on inter-rater reliability. A decade later, Zucker, Bradley, and Lowry Sullivan (1996b) examined the relationship between GID and SAD in 115 boys (M age, 6.3 years), of whom 73 (63.5%) met the full diagnostic criteria for GID and the remaining 42 (36.5%) were subthreshold for the diagnosis. To assess the presence of SAD, Zucker et al. developed a 21-item parent-report interview based on the DSM-III diagnostic criteria. The items assessed nine content domains which reflected the DSM-III criteria for SAD. Questions were phrased such that they could be answered by mothers as “Yes,” “Sometimes,” or “No.” Zucker et al. used conservative and liberal criteria to assign a diagnosis of SAD that differed in terms of the frequency of the symptoms reported. A conservative diagnosis was given if the mother answered “Yes” to questions in three of the nine content domains. A liberal diagnosis was given if the mother answered “Yes” or “Sometimes” in three of the nine content domains. Using the conservative criterion for SAD, there was no significant association between the presence of GID and SAD. A significant association existed when the liberal criterion was used. Of the 73 boys who meet full criteria for GID, 47 (64.4%) also met the criteria for SAD. In contrast, only 16 (38.1%) of the 42 boys who were subthreshold for the diagnosis of GID also met criteria for SAD.

A limitation of Coates and Person's (1985) and Zucker et al.'s (1996) study is that neither included a group of clinical control participants referred for reasons other than GID.

Nonetheless, the rates of SAD obtained in these studies are higher than the prevalence rates of SAD in children (for a review, see Masi, Mucci, & Milliepedi, 2005) and suggests that SAD may be overrepresented in boys with GID.

A recent line of research has led some authors to conclude that elevated levels of separation anxiety in childhood may be a component of the more general pattern of childhood femininity seen in some homosexual men (for a review, see VanderLaan, Gothreau, Bartlett, & Vasey, 2011a). Using a retrospective design, VanderLaan, Gothreau, Bartlett, and Vasey (2011b) found that homosexual men recalled, on average, significantly higher levels of separation anxiety compared to heterosexual men but similar to those of women. For the homosexual men but not heterosexual men, increases in recalled childhood femininity were associated with increases in separation anxiety. There is also cross-cultural support for this finding. Vasey, VanderLaan, Gothreau, and Bartlett (2011) found that Samoan *fa'afafine* recalled significantly more childhood separation anxiety compared to Samoan women and (heterosexual) men. These results raise the question of whether boys with GID who develop a homosexual sexual orientation would have experienced more separation anxiety in childhood compared to those who develop a heterosexual sexual orientation. None of the prospective studies on boys with GID have specifically examined this.

Researchers in The Netherlands systematically assessed the prevalence of DSM diagnoses in children with GID using a structured parent-report interview (Wallien, Swaab, & Cohen-Kettenis, 2007). Wallien et al. compared 120 children referred to a specialized gender identity clinic and diagnosed with GID (86 boys, 34 girls; age range, 4-11 years) to 47 children

(37 boys, 10 girls) referred to an ADHD clinic and who served as a clinical control group. Of the 120 children with GID, 62 (51.6%) met criteria for a DSM diagnosis other than GID. There was no significant difference between the GID and ADHD children on number and type of comorbid diagnoses. Of the 86 GID boys, 48 (55.8%) met criteria for a diagnosis other than GID. Of these, more than half ($n = 26$, 56.1%) met criteria for an anxiety disorder (mostly specific phobia), 22 (25.5%) met criteria for a disruptive disorder (e.g., oppositional defiant disorder), and 4 (4.7%) met criteria for a mood disorder. In contrast to the studies by Coates and Person (1985) and Zucker et al. (1996b), only 5 (5.8%) of boys with GID met criteria for SAD.

The above described associated psychopathology in children with GID can be understood in several ways. First, as noted earlier, it may be the result of social ostracism (Zucker, 2005c). Second, it has been shown that behavior problems in gender-referred children may be significantly associated with measures of parental psychopathology and this may reflect generic familial vulnerability to psychopathology (Zucker & Bradley, 1995; Zucker et al., 2003). Third, associated psychopathology in children with GID may be implicated in the etiology of GID and, therefore, may contribute to its genesis (Coates & Person, 1985; Zucker et al., 2012b). Regardless of the mechanisms underlying the relationship between childhood cross-gender behavior and general behavior problems in gender-referred children, it raises the question of whether the associated psychopathology in childhood is related to long-term psychosexual and psychiatric outcomes, a question the present study will attempt to address.

1.10.2 Adolescents and Adults with GID

CBCL data suggest that adolescents with GID have significantly higher levels of behavioral problems (e.g., Internalizing T score) and poorer peer relations compared to children with GID (Zucker, Owen, Bradley, & Ameeriar, 2002). As discussed earlier, this “age effect”

could represent a proxy for social ostracism (i.e., youth with gender identity issues encounter more problems in their social relationships as they age). Similar to that observed in children with GID, gender-referred adolescents are as likely to have as many behavior problems and similar peer relations as other clinically referred adolescents (i.e., referred for reasons other than gender) and to have considerably more behavioral problems and poorer peer relations than nonreferred adolescents (Zucker et al., 2012b; for a review, see Zucker, 2006c).

The presence of comorbid psychiatric diagnoses in adolescents with GID is an extremely important clinical issue as it can influence decisions regarding treatment recommendations (Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008; Zucker et al., 2011). Only one study has systematically examined comorbidity of DSM diagnoses in adolescents with GID. Using a structured parent-report interview, de Vries, Doreleijers, Steensma, and Cohen-Kettenis (2011b) examined the presence of DSM diagnoses (other than GID) in 105 gender referred adolescents (53 males, 52 females; M age at assessment, 14.6 years). Of the 105 adolescents, 32.4% met criteria for at least one DSM diagnosis other than GID, which is lower than the obtained prevalence rate of comorbid diagnoses of 52% seen in children with GID (see Wallien et al., 2008). These results are, therefore, in contrast to studies showing more problem behaviors in adolescents compared to children. For the entire sample, the most common disorders were social phobia (9.5%) and major depression (8.6%). The presence of comorbid diagnoses did not vary according to GID diagnosis (i.e., full criteria versus sub-threshold). Of the 53 boys in the study, 39.6% met criteria for at least one concurrent disorder. Social phobia, major depression, and oppositional defiant disorder were the most common diagnoses. Further, the biological males in this study were at increased odds of having a mood or anxiety disorder compared to the natal females. de Vries et al. suggested that perhaps natal males with GID show patterns of

psychopathology most typically associated with their desired gender (i.e., females). The most prominent limitation of this study was that parents, not the adolescent themselves, were the informants. This might have resulted in an underestimate of some diagnoses, such as alcohol or substance abuse and, by extension, an underestimate of the prevalence of comorbid diagnoses in adolescents with GID.

Comorbidity with other Axis I psychiatric disorders have been examined in adults with GID. The rates obtained have varied across studies. Cole, O'Boyle, Emory, and Meyer (1997) relied on historical information to assess comorbidity in 318 male-to-female transsexuals seen in a gender identity clinic. Only 6% of the patients reported a history of treatment for an Axis I disorder other than substance use or GID. The most common comorbid diagnosis was major depression. Other studies have used unstructured and semi-structured interviews to assess for other psychiatric conditions and these have typically founds higher rates of comorbidity. In some studies, data were reported for male-to-females and females-to-males combined. Bodlund and Armelius (1994) reported that 44% of a mixed group of male-to-female and female-to-male had another Axis I diagnosis other than GID. Haraldsen and Dahl (2000) reported similar results: in a mixed group of male-to-female and female-to-male transsexuals that included both pre-operative (i.e., applied for sex reassignment surgery) and post-operative patients (i.e., completed sex reassignment surgery), 33% met criteria for another Axis I diagnosis. De Cuypere, Jannes, and Rubens (1995) reported a lower rate of comorbidity. Only 23% of the male-to-female patients in their study met criteria for another Axis I disorder. In a recent study of adult patients with GID in Japan, Hoshiai et al. (2010) reported that 18% of the male-to-female patients had another Axis I diagnosis. Across these studies, the most common comorbid diagnoses were a mood or anxiety disorder. Hoshiai et al. reported that 76% if the male-to-female patients reported a lifetime

history of suicidal ideation. De Cuypere, Jannes, and Rubens (1995) and Verschoor and Poortinga (1988) reported high rates of lifetime suicide attempt in their samples of male-to-female patients, 54% and 19% respectively.

Prevalence estimates of comorbid substance use in male-to-female adults with GID have varied. None of the male-to-female patients in Hoshiai et al.'s (2010) study had comorbid substance-related disorders. In contrast, Cole et al. (1997), Hepp, Kraemer, Schnyder, Miller & Delsignore (2005), and De Cuypere et al. (1995) reported fairly high lifetime prevalence figures of substance abuse in the male-to-female patients: 29%, 50%, and 50%, respectively.

De Cuypere et al. (1995) reported personality disorders in 70% of the male-to-female patients in their sample. Most other studies, however, have found lower rates of comorbid Axis II disorders. For example, Hepp et al. (2005), Bodlund and Armelius (1994), and Haraldsen and Dahl (2000) reported prevalence rates of 42%, 33%, and 20% respectively. Of note, these latter studies reported on mixed groups of male-to-female and female-to-male patients. With the exception of De Cuypere et al.'s study, these rates are similar to those seen in other clinical populations but higher than in nonclinical populations (e.g., Newton-Howes et al., 2010; Zimmerman, Rothschild, & Chelminski, 2005).

1.10.3 Suicidality and Victimization in Transgendered Populations

Even among youth unselected for their gender identity, the presence of gender atypical behavior appears to be associated with poorer well being (Rieger & Savin-Williams, 2012) and places these youth at higher risk for victimization compared to gender-typical youth. Thus, transgender youth are particularly vulnerable to victimization because of their atypical gender role presentation (for a discussion, see Stieglitz, 2010). Nuttbrock et al. (2010) found that 50.1% of male-to-female transgendered adults (from a sample of 517) experienced physical abuse while

78.1% experienced verbal abuse that was related to their gender identity/gender role. In an earlier study, Grossman, D'Augelli, and Salter (2006) found that 87% of male-to-female transgendered youth had experienced some type of victimization. These percentages appear to be higher than the estimated victimization rates for youth in North America of 50%-62% (e.g., Kilpatrick, Saunders, & Smith, 2002; Romano, Bell, & Billette, 2011; Saunders, 2003).

A number of population-based studies have found that transgendered youth/adults may be at an increased risk for suicide attempts compared to youth in the general population (for a review, see Haas et al., 2011). It has been estimated that 3.13%-4.6% of adults in the United States have made at least one suicide attempt (Kessler, Borges, & Walters, 1999; Weissman et al., 1999). In staggering contrast, studies of community samples of youth who self-label as transgendered have found that approximately 30-40% have made at least one suicide attempt (Clements-Nolle, Marx, & Katz, 2006; Grossman & D'Augelli, 2007; Maugen & Shipherd, 2010).

Transgendered individuals may be at even greater risk for suicide ideation and attempts than homosexual males (Mathy, 2003) and this may be directly related to discrimination and victimization pertaining to their gender atypical behaviors (Clements-Nolle et al., 2006; Nuttbrock et al. 2010). Given that the majority of boys with GID later develop a homosexual sexual orientation with desistence of GID, it has been suggested that they may share some of the same risk factors that have been identified in gay and lesbian adolescents, including stigmatization, rejection by the peer group, discrimination, and mental health difficulties (see e.g., D'Augelli, 2002; Lombardi, Wilchins, Priesing, & Malfouf, 2001; Mathy, 2003; Meyer, 2003; Morrow, 2004; Sandfort, Bakker, Schellevis, & Vanwesenbeeck, 2006; Savin-Williams & Ream, 2003). A large body of evidence, including well conducted epidemiological studies

indicates that individuals from sexual minority populations are at an increased risk for various mental health difficulties, most notably depression, suicide, anxiety, and substance use, compared to their heterosexual counterparts (Cochran, 2001; Cochran & Mays, 2000; Cochran, Sullivan, & Mays, 2003; D'Augelli, 2002; Faulkner & Cranston, 1998; Ferguson, Horwood, & Beautrais, 1999; Gilman et al. 2001; King et al., 2008; Meyer, 2003; Remafedi, French, Story, Resnick, & Blum, 1998), with prevalence rates of suicide attempts ranging from 23% to 42% (D'Augelli & Hershberger, 1993; D'Augelli, Hershberger, & Pilkington, 1998, 2001; Safren & Heimberg, 1999; for a review, see McDaniel, Purcell, & D'Augelli, 2001). Furthermore, studies have found that the increased risk for suicide attempts among sexual minority youth is maintained even after controlling for substance abuse and other psychiatric comorbidity, such as depression (e.g., Herrell et al., 1999). That an association exists between homosexuality and mental health risk is now generally accepted (see meta-analysis by King et al., 2008).

1.1.1 A Conceptual Framework for the Present Study

The extent to which childhood behavior is predictive of behavior in adulthood has been a central question in the field of developmental psychology. Historically, researchers took a retrospective approach to examining the relationship between adult and child psychopathology. The major methodological limitation with retrospective studies, however, pertains to possible distortions in memory in recalling childhood symptoms or behavior (e.g., Verhulst, 1995). This limitation, combined with the increased recognition that some childhood problems continued into adulthood while others did not, argued for a prospective approach (Achenbach, 1997) and resulted in a wave of prospective studies which examined the developmental course of psychopathology in children.

Prospective studies of children with a particular disorder have found that some children continue to have the same disorder in adolescence and adulthood. Other children, however, show a desistence of the disorder from childhood to adolescence and, therefore, demonstrate discontinuity of the disorder over time (Maughan & Rutter, 2008). Thus, children with the same diagnosis in childhood can have multiple outcomes in adolescence and adulthood, which is commonly referred to as multifinality (Cicchetti & Rogosch, 1996). A longitudinal approach is necessary if one is to understand both continuities and discontinuities in psychopathology over time (Verhulst & Koot, 1991).

These developmental psychopathology concepts are particularly relevant to any prospective follow-up studies of boys with GID. The extant literature on boys with GID indicates that most grow up to feel comfortable with their biological sex and show a desistence of GID. Of the boys who show desistence of GID, most develop a homosexual sexual orientation and a minority develops a heterosexual sexual orientation. Thus, it appears that only a minority of boys with GID show persistence of the disorder into adolescence and adulthood. Therefore, within a group of boys with GID, discontinuity of the disorder from childhood to adolescence appears to be the most common developmental trajectory; however, there are multiple long-term outcomes for boys with GID. To understand this finding, it is necessary to conduct within-group analyses (McNeil & Kaij, 1979) to identify childhood factors that can predict outcome in adolescence and adulthood (e.g., with regard to persistent GID vs. desistent GID). Further, the percentage of children with GID who show persistent gender dysphoria into adolescence and adulthood is higher than the estimated prevalence rate of GID in the general population. Children with GID, then, can be conceptualized as “high-risk” for GID in adulthood when compared to children without GID.

The present study can be conceptualized as a within-group comparison of a group of children “at risk” for GID to develop an understanding of the childhood factors that can predict the various observed outcomes. Four decades ago, Green (1970) recognized that the developmental picture leading to “transsexualism” in adulthood can only be clearly understood by conducting longitudinal research. On understanding the development of adult transsexualism, Green wrote, “One way is to study a group of young children who would appear to be of high risk with respect to later manifestation of anomalous sexual and gender behavior, and to study their families. Most adults who request sex reassignment report difficulties in adopting appropriate gender-typic behavior during childhood (p. 271).”

Several studies using prospective designs have been conducted to examine predictors of outcome in children with other psychiatric disorders, including schizophrenia (Werry & McClellan, 1991), bipolar disorder (Geller, Fox, & Clark, 1993; Werry, McClellan, & Chard, 1991), attention deficit-hyperactivity disorder (Dalsgaard, Mortensen, Frydenberg, & Thomsen, 2002), conduct disorder (see Robins, 1966), and pervasive developmental disorders (Szatmari, Bryson, Boyle, Streiner, & Duku, 2003). Notably, in adults with antisocial disorder, a similar disjunction between retrospective and prospective studies as observed in GID is also found: severely antisocial adults were antisocial children; however, only about half of antisocial/conduct disordered children grow up to become antisocial adults (for a review, see Maughan & Rutter, 2008). Longitudinal studies have also been conducted on children identified as “at-risk” for developing schizophrenia later in life, with the goal of identifying predictors of within-group outcome (i.e., development of schizophrenia versus no schizophrenia later in life) (Erlenmeyer-Kimling et al., 1997; Neale & Weintraub, 1975;). These studies have suggested attempts to predict outcome should include demographic, psychosocial, and psychological factors.

1.11.1 Rationale for the Present Study

There are several reasons why a systematic examination of the long-term outcome of boys with GID is urgently needed, with both theoretical and clinical implications. The follow-up studies on boys with GID have focused predominantly on examining outcome vis-à-vis gender identity and sexual orientation. At present, very little is known about the long-term psychiatric functioning among boys with GID.

Although a large majority of boys with GID no longer have the disorder in adulthood, there is variation in the rates of persistence obtained in follow-up studies. Additional follow-up studies are needed to better clarify what proportion of boys may persist in having the disorder in adolescence and adulthood. Further, there are very limited data on childhood characteristics that may differentiate persisters from desisters. For example, it appears that children with more severe cross-gender identification are more likely to show persistence of GID compared to children who are less severe (Wallien & Cohen-Kettenis, 2008). However, other childhood factors may also contribute to the developmental course of GID. None of the follow-up studies to date have systematically conducted an evaluation of childhood demographic, psychosocial, and psychological variables and their role in the persistence and desistence of GID. Green (1970) stated, “The developmental picture leading to adult transsexualism remains smudgy” (p. 271). Four decades later, the picture is still “smudgy.”

The identification of predictors of GID outcome also carries clinical implications. In children with GID who appear to be on a trajectory for GID in adolescence and adulthood, intervention efforts can attempt to steer them away from a transsexual outcome onto one in which comfort with one’s biological sex is the outcome. The rationale for such an intervention is the observed complexity of embarking on a life course of cross-sex hormonal and surgical

treatment combined with the pervasive social discrimination and victimization that many people with gender dysphoria encounter (Zucker, Drummond, Bradley, & Peterson-Badali, 2009).

Green (2008), more directly, expressed that living as a homosexual adult is generally easier than living as a transsexual. Some clinicians have argued for early recognition of children who may persist in their gender dysphoria, but from a different standpoint. If a clinician is certain that a child with GID is committed to a pathway leading to transsexualism (i.e., persisting GID), interventions with gonadotropin releasing hormone (GnRH) blockers (commonly referred to as “puberty blockers”) could be used to delay the onset of puberty (Wallien & Cohen-Kettenis, 2008).

It is also clinically relevant to examine childhood factors that may predict outcome with regard to psychological functioning in adolescence and adulthood. If it were possible to identify children who may be at risk for developing psychiatric problems in adulthood, treatment can also focus on reducing the risk for psychopathology. In the field of developmental psychopathology, in general, the identification of predictors of change in psychopathology has been regarded theoretically important for advancing our knowledge of the development of psychopathology and as clinically relevant for informing treatment guidelines (Mathijssen, Koot, & Verhulst, 1999).

The present study is also urgently needed given the intense controversy in the field regarding best treatment practice for children with GID. While some parents seek therapeutic support that helps their child feel more comfortable with a gender identity that matches the child’s birth sex, a more extreme group of parents, and some therapists, actively promote an early social transition in the child, sometimes as young as preschool (Zucker et al., 2009). Unfortunately, there are no comparative data on the effects of these treatment approaches on long-term psychosexual and psychological outcome of children with GID. Given that the follow-

up studies conducted thus far have found that most children with GID show a desistence, treatment approaches, particularly those that espouse early transitioning, need to be evaluated. Although the present study does not include an evaluation of therapeutics, data on persistence, desistence, and the factors that can predict outcome may, in the interim, inform treatment approaches.

Beyond the contextual importance of this study, the strong methodological design warrants specific mention. This present study differs from previous follow-up studies in several ways. First, the number of boys in our sample was considerably larger than the sample sizes of its predecessors. Second, I have extensive assessment data on psychological functioning in childhood and at follow-up. Third, at follow-up, cross-informant data (via parent-report) on psychological functioning and gender role are available. Fourth, the present study includes a measure of social desirability, which is a particularly important construct to measure in studies that examine gender identity and sexual orientation.

1.11.2 Goals of the Present Study

The first goal of the study was to provide descriptive data on the long-term outcome of boys with GID with regard to four possible outcomes: (1) persistence of gender dysphoria with a bisexual/homosexual sexual orientation, (2) persistence of gender dysphoria with a heterosexual sexual orientation, (3) desistence of GID with a bisexual/homosexual sexual orientation, and (4) desistence of GID with a heterosexual sexual orientation.

The second goal of the study was to provide descriptive data on the long-term psychiatric outcomes of boys with GID in terms of DSM psychiatric diagnoses and general behavior problems, both for the overall group of boys and according to their psychosexual outcome.

The third goal of the study was to identify childhood factors which can predict outcome at follow-up with regard to gender identity and sexual orientation. This included a systematic examination of demographic, psychological, and psychosocial variables as potential predictors of outcome.

The fourth goal of the study was to provide preliminary data on adult victimization experiences of boys with GID and its relationship to their psychiatric functioning.

Chapter 2

Method

2.1 Participants

The participants were biological males who had been referred to and then assessed in the Gender Identity Service, Child, Youth, and Family Program at the Centre for Addiction and Mental Health (CAMH) in Toronto, Ontario during their childhood and were adolescents or adults at the time of follow-up. Data collection occurred over three decades, 1986-2011 (Table 1).

Participants entered the follow-up study through two methods of recruitment. Most participants were recruited through routine contact for research follow-up. From 1986-2011, there were two main waves of participant recruitment through research contact, from 1986-1993 and, more recently, from 2009-2011.¹⁵ In addition, during the period of data collection, some adolescents who had been assessed in the clinic during childhood contacted the service for clinical reasons (e.g., persistent gender dysphoria, emerging sexual identity, or other clinical issues). These participants were informed about the opportunity to participate in the follow-up study and subsequently completed the study protocol. The majority of the patient-initiated participants had contacted the clinic between the two main waves of research recruitment. Thus, from 1994-2008, the participants who entered the study were primarily those who had contacted the service for clinical reasons. As such, the final study sample consisted of participants who entered the study through standard research contact or following participant-initiated involvement with the clinic.

¹⁵ During this wave of systematic data collection, there was a relatively greater focus on recruitment during 2009 compared to 2010. In 2010, recruitment occurred primarily during the first 6 months of the year. Thus, a larger number of participants were assessed in 2009 compared to 2010.

Table 1
Distribution of Recruitment Across Data Collection Period

Year	Number of participants recruited	Method of Study Entry	
		Research	Clinical
1986	8	8	0
1987	7	7	0
1988	8	8	0
1989	3	3	0
1990	4	4	0
1991	4	4	0
1992	0	0	0
1993	3	3	0
1994	0	0	0
1995	2	1	1
1996	0	0	0
1997	1	0	1
1998	2	1	1
1999	0	0	0
2000	2	0	2
2001	1	0	1
2002	6	2	4
2003	5	1	4
2004	3	0	3
2005	3	1	2
2006	2	1	1
2007	2	0	2
2008	2	0	2
2009	40	36	4
2010	25	23	2
2011	6	4	2

2.1.1 Routine Contact for Research

A chart review was conducted of all boys (range, 3-12 years) assessed in the Gender Identity Clinic Service at the CAMH since 1975 to identify eligible participants. Between 1975 and 2009, the clinic evaluated 463 boys referred for gender identity issues. To participate in the follow-up study, patients from this sample had to be at least 16 years of age. Using this cut-off,

the chart review identified 294 eligible participants, of which contact was attempted in 132 cases. For the remaining 162 cases, contact was not attempted due to lack of study resources and time constraints.

Of the 132 cases where contact was attempted, 19 (14.3%) potential participants could not be reached/traced through previous addresses, registrars, and personal contacts (e.g., the patient and/or family had moved and a current telephone number, mailing address, or e-mail could not be identified). Initial telephone contact was first made with the parents because participants were minors at the time of the childhood assessment and may have had no recollection of their clinic attendance (see Appendix C for phone script). In general, the response from parents and participants was positive. Of the 113 patients where contact was successful, 79 (69.9%) agreed to complete the study protocol and came into the clinic for a face-to-face assessment. In 28 (24.8%) cases, some follow-up data on gender identity and sexual orientation were provided over the phone by the parents or the patients themselves or were obtained through a chart review. For a variety of reasons, these 28 participants did not complete the standard follow-up assessment (e.g., geographic limitations, too busy). Appendix D summarizes the information acquired during a telephone conversation with the parent of a follow-up participant and serves as an exemplar of the information provided by parents, and which was used as the basis for group classification at follow-up. In the remaining 6 (5.3%) cases, either the parents did not allow us to speak to their now grown up child or the potential participant himself declined to participate in the study. In total, 107 participants entered the study through routine research recruitment.

2.1.2 Participant-Initiated Clinical Contact

An additional 32 participants were recruited into the study after they had contacted the Gender Identity Service for clinical reasons. In 7 cases, either the participant or the parents contacted the clinic due to persistent gender dysphoria. In 6 cases, the clinic was contacted because either the participant or the parent was concerned about sexual orientation and in 1 case there was concern about gender dysphoria and sexual orientation. Lastly, in the remaining 18 cases, the participants or parents contacted the clinic for other heterogeneous clinical concerns, including depression, substance abuse, parent-child conflict, and conduct problems. Appendix E lists the reasons for contacting the clinic for each of the 32 participants.

Some of the participants who contacted the clinic were younger than 16 years of age. It is important to note that all participants were aware that completing the follow-up study was voluntary and a decision to decline participation in the study would not have affected their involvement with the clinic. Of these 32 participants, 31 completed the standard follow-up protocol and 1 participant provided some data on gender identity and sexual orientation but did not complete the formal study.¹⁶

¹⁶Using *t*-tests, the 107 participants who entered the study through routine research contact were compared to the 32 participants who were recruited into the study after they had re-contacted the clinic for clinical reasons on childhood demographic variables (age at assessment, IQ, social class, marital status, ethnicity), CBCL behavior problems in childhood (Internalizing *T* score, Externalizing *T* score, Total *T* score), and nine measures of childhood sex-typed behavior. There were no significant differences between the two groups on the demographic variables of age at assessment, social class, ethnicity or marital status ($ps > .05$). The comparison on childhood IQ approached significance, $t(137) = 1.97, p = .051$, with the routine research entry participants having, on average, a higher IQ than the clinical entry participants. On the CBCL, there was a significant difference on Internalizing problems only, $t(137) = -2.02, p = .046$, with the clinical entry participants rated by their parents as having more internalizing problems compared to the research entry participants. Of the nine measures of childhood sex-typed behavior, the two groups differed significantly on three: (1) free play, $t(119) = -2.11, p = .037$, (2) Gender Identity Interview, $t(83) = -2.09, p = .04$, and (3) Gender Identity Questionnaire for Children, $t(95) = 2.39, p = .019$, with the clinical entry participants having, on average, more childhood cross-gender behavior than the research entry participants. Of the 32 clinical entry participants, 8 had re-contacted the clinic because of gender dysphoria. The above described comparisons were repeated to compare the research and clinical entry participants but with these 8 participants excluded. With the 8 participants who contacted the clinic for gender dysphoria removed, there were no significant group differences on demographic variables, CBCL behavior problems, and measures of childhood sex-typed behavior (all $ps > .05$).

2.1.3 Participation Rate

In total, 145 participants were approached about participating in the follow-up study, either through routine contact ($n = 113$) or following their clinical involvement with the Gender Identity Service ($n = 32$). Six participants declined, which yielded a participation rate of 95.9%.

2.1.4 Demographic Characteristics of Participants

The demographic characteristics of the participants in childhood and at follow-up are shown in Table 2. The GID diagnosis in childhood was based on the *DSM* (3rd ed. [DSM-III]; 3rd ed., rev. [DSM-III-R]; or 4th ed. [DSM-IV]; American Psychiatric Association [APA], 1980, 1987, and 1994, respectively) criteria applicable at the time of assessment. A total of 88 (63.3%) boys met complete DSM criteria for GID in childhood. The remaining 51 (36.7%) boys were subthreshold for a DSM diagnosis, but all had some indicators of GID, and, based on the historical information provided during the assessment, some would have met the complete DSM criteria at some point in their lives prior to their assessment in childhood.

The mean age of assessment in childhood was 7.49 years ($SD = 2.66$; range, 3.33-12.99) and the mean age at follow-up was 20.58 ($SD = 5.22$; range, 13.07-39.15). The mean time interval between childhood assessment and follow-up was 12.88 years ($SD = 6.07$; range, 2.77-29.29).

2.2 Procedure

The study was approved by the Institutional Review Boards at the CAMH and the University of Toronto. The majority of participants who completed the face-to-face assessment were evaluated on a single day. Three participants were seen twice. In these instances, the participants completed the self-report measures during their second visit as the complexity of their clinical presentation extended the duration of the assessment. Participants were provided a

Table 2
Demographic Characteristics (N = 139)

Characteristic	M	SD	Range	%
From childhood				
Age (in years)	7.49	2.66	3.33-12.99	
Year of birth	1981.87	7.50	1966-1996	
Year of assessment	1989.36	7.50	1975.42-2004.84	
IQ ^a	105.93	15.47	69-138	
Social Class ^b	40.74	15.15	8.0-66.0	
Marital Status ^c				
Two-parent family				64.7
Other				35.3
Caucasian				84.9
At follow-up				
Age (in years)	20.58	5.22	13.07-39.15	
Follow-up interval (in years) ^d	12.88	6.07	2.77-29.29	
IQ ^{a,e,f}	105.88	16.03	65-138	

^aFull-Scale IQ was obtained with age-appropriate Wechsler intelligence scales.

^bHollingshead's (1975) Four Factor Index of Social Status (absolute range: 8-66), which is based on educational level and occupation.

^cOther included the following family constellations: single parent, separated, divorced, living with relatives, or in the care of a child protection agency.

^dInterval denotes the time between childhood assessment and follow-up assessment.

^eFull Scale IQ estimated using four subtests: Vocabulary, Comprehension, Block Design and Object Assembly.

^fIQ were only available for participants who completed the face-to-face assessment. Of these, scores were not available for 1 participant.

stipend for their participation in the follow-up assessment and reimbursement for travel expenses.

All participants who completed the face-to-face assessment gave written informed consent prior to their involvement in the follow-up assessment (see Appendix F). Participants were explained their right to participate, their right to withdraw at any time during the study, and assured anonymity. Concerns about emotional distress (e.g., endorsement of suicidality in the psychiatric interview) were addressed; although no participants required acute immediate care, there were instances in which intervention or clinical care was required. The majority of the

follow-up procedures were conducted by the author of this thesis ($n = 71$) under the supervision of Dr. Kenneth Zucker. However, for participants assessed prior to 2009, the study procedures were carried out by Dr. Kenneth Zucker ($n = 68$).

Participants who completed the face-to-face interview responded positively to the assessment process. With one exception, rapport with the participants appeared to be good. At the time of follow-up, two participants were currently being seen in our clinic for therapy.

2.3 Measures

2.3.1 *Childhood Assessment*

2.3.1.1 *Cognitive Functioning*

Based on the age of clients at the time of assessment, the appropriate version of the Wechsler Intelligence Scale for Children was administered (WISC-R, WISC-III, WISC-IV or the WPPSI-R).¹⁷ Full scale IQ scores were used to characterize level of cognitive functioning.

2.3.1.2 *Sex-typed Behavior*

A variety of methods and measures were used to assess sex-typed behavior in childhood (i.e., gender identity and gender role), which are summarized in Table 3. A total of five child informant and two parent informant measures were used to assess the participants' sex-typed behavior in childhood: (1) Draw-a-Person test (Zucker, Finegan, Doering, & Bradley, 1983); (2) a free-play task (Zucker, Doering, Bradley, & Finegan, 1982); (3) the Playmate and Playstyle Preferences Structured Interview (Fridell, Owen-Anderson, Johnson, Bradley, & Zucker, 2006); (4) sex-typed responses on the Rorschach test (Zucker, Lozinski, Bradley & Doering, 1993); (5) the Gender Identity Interview for Children (Wallien et al., 2009; Zucker et al., 1993); (6) The Gender Identity Questionnaire for Children (Johnson et al., 2004); and (7) a measure of activity

¹⁷Correlation among subtests scores, index, scores and full scale IQ across versions of the WISC ranges from medium to high (Wechsler, 2003).

Table 3
Measures of Gender Identity and Gender Role in Childhood

Measure	Informant	Mode	Description of Variables
Draw-a-Person (Jolles, 1952 ; Zucker, Finegan, Doering, & Bradley 1983)	Child	Test	Sex of first drawn person.
Free-play task (Reckers & Yates, 1976; Zucker, Doering, Bradley & Finegan, 1982)	Child	Observation	Difference between cross-sex and same-sex play. Positive score indicates more cross-sex play.
Rorschach inkblot test (Zucker, Lozinski, Bradley, & Doering, 1992)	Child	Test	Difference between number of same-sex and cross-sex responses. A higher score indicates more cross-sex than same-sex responses.
Gender Identity Interview (Wallien et al., 2009; Zucker et al., 1993)	Child	Interview	Semi-structured gender identity interview schedule with questions that establish gender dysphoric feelings and confusion one's gender status. Higher scores reflect more gender-atypical responses.
Playmate and Playstyle Preferences Structured Interview (Alexander & Hines, 1994; Fridell, Owen-Anderson, Johnson, Bradley, & Zucker, 2006)	Child	Test	Yields two scores: cross-sex peer preference and cross-sex play preference. A higher score indicates more cross-sex playmate/peer choices.
Gender Identity Questionnaire for Children (Johnson et al., 2004; Zucker et al., 2003)	Parent	Questionnaire	Higher scores reflect more cross-gendered behavior.
Temperament: Activity Level/Extraversion (Zucker & Bradley, 1995 pp. 189-193)	Parent	Questionnaire	Higher ratings indicate elevated activity levels and more rough-and-tumble play.

Note. With the exception of Draw-a-Person, which is a categorical variable, variables based on other measures of childhood sex-typed behavior are continuous.

level/extraversion (Zucker & Bradley, 1995). Some of these measures have been designed to assess gender identity constructs or a child's general discomfort with his or her gender status, as well as gender role behaviors (e.g., toy preferences, fantasy play). Other measures assess well-established normative gender differences for dimensions of temperament that included ratings of activity level and involvement in rough-and-tumble play (see review in Zucker, 2005b).

2.3.1.3 Behavior Problems

The Child Behavior Checklist (CBCL; Achenbach, 1991; Achenbach & Edelbrock, 1983) was completed by a parent or guardian during the child's initial assessment. This measure is a standardized parent-report questionnaire for ratings of behavior problems in children 4 to 18 years of age. It consists of 118 behavior problems that are rated on a 3-point scale (0 = not true, 1 = sometimes true or somewhat true, 2 = very true or often true). The questionnaire identifies two "broad-band" factors, "Internalizing" and "Externalizing," that assess dimensions of child psychopathology. Internalizing disorders are described as covert emotional disturbances (e.g., depression, social withdrawal, anxiety) and the Externalizing disorders are described as disorders of overt conduct (e.g., aggression, hyperactivity). Parent ratings on the CBCL yield *T* scores for Total, Internalizing, and Externalizing problems. Reports indicate extensive evidence for the reliability and validity of the CBCL as an index of behavioral psychopathology in clinical and nonclinical populations (Achenbach, 1985, 1991; Achenbach & Edelbrock, 1983; Achenbach, McConaughy, & Howell, 1987). The intra-class correlations for individual items were more than .90. Test-retest reliability over a one-week period was .89, and inter-parent agreement for total behavior problem scores was .66. Furthermore, the long-term stability estimates for total behavior problem scores over 3-,

6-, and 18-month periods were .74, .60, and .46, respectively (Achenbach & Edelbrock, 1983). The CBCL discriminates well between children referred to mental health agencies from demographically-matched non-referred children (Achenbach & Edelbrock, 1983).

2.3.1.4 Peer Relations

Zucker, Bradley, and Sanikhani (1997) constructed a three-item Peer Relations Scale derived from the CBCL using Items 25, (“Doesn’t get along with other kids”), 38 (“Gets teased a lot”), and 48, (“Not liked by other kids”). Based on maternal ratings on the CBCL, both boys and girls with GID had poorer peer relations than did their siblings. Cronbach’s alpha was .81 and the mother-father correlation for the scale was .66 ($n = 312$, $p < .001$). The Peer Relations Scale was subsequently used in comparative study of children and adolescents with GID (Zucker, Owen, Bradley, & Ameeriar, 2002) where it was the strongest predictor of behavioral psychopathology on the CBCL for both children and adolescents. Cohen-Kettenis et al. (2003) used the Peer Relations Scale in a cross-clinic study in which children with gender identity issues seen at the Gender Identity Service at the CAMH were compared to children with gender identity issues seen at the Gender Clinic housed within the Department of Child and Adolescent Psychiatry at the University Medical Center Utrecht (The Netherlands) on demographic characteristics, social competence, and behavior problems. Across both clinics, boys with gender identity issues had poorer peer relations than did girls.

2.3.2 Follow-up Assessment

Table 4 summarizes the follow-up assessment protocol. The gender identity and sexual orientation measures, along with self-report measures of behavior problems, are used as part of the current standardized clinical assessment of adolescents referred to the Gender Identity Service (Zucker, 2005b; Zucker et al., 2012b; Zucker & Bradley, 1995). The

victimization and suicidality questionnaires were novel to this follow-up evaluation, as was the standardized interview schedule to assess the presence of DSM psychiatric disorders.

All interviews were conducted in a private office. The follow-up assessment protocol was administered in the following order to all participants: (a) cognitive testing, (b) psychiatric diagnostic interview, (c) semi-structured clinical interview, and (d) self-report questionnaires. The semi-structured clinical interview consisted of four parts: (a) the participant's current functioning (e.g., family, school, and work), (b) recollections of and thoughts about the childhood assessment and childhood gender role/gender identity, (c) current gender identity, and (d) sexual orientation in fantasy and behavior. The semi-structured interview always preceded the self-report questionnaires and was audiotaped, except in one instance where the participant did not give consent. The self-report questionnaires provided an immediate cross-check of the interview and served additional quantitative purposes. The contents of the follow-up assessment are described below.

2.3.2.1 Cognitive Functioning

Four subtests from the age-appropriate version of the Wechsler Intelligence Scales were administered (Vocabulary, Comprehension, Block Design, and Object Assembly). The scaled scores from these subtests were used to provide an estimated IQ score for cognitive functioning (Sattler, 2001). Data collection occurred over a period of 24 years. During this time, the Wechsler Intelligence Scales underwent revisions and the most recent version at the time of assessment was used for cognitive testing. As a result, over the period of data collection, several versions of the Wechsler scales were used. Participants 17 years or older were administered the Wechsler Adult Intelligence Scale-Revised ($n = 8$; WAIS-R; Wechsler, 1981), the Wechsler Adult Intelligence Scale-Third Edition ($n = 16$; WAIS-III;

Table 4
Follow-up Assessment Protocol

Variable	Measure
Cognitive Functioning	Selected subtests from the WAIS-III, WAIS-IV, WISC-III, or WISC-IV
Psychiatric and Behavioral Functioning	Diagnostic Interview for Children and Adolescents (Herjanic & Reich, 1982) or Diagnostic Interview Schedule-Version III-A (Robins & Helzer, 1985) Parent report: Child Behavior Checklist (Achenbach, 1991) or Adult Behavior Checklist (Achenbach & Rescorla, 2003) Self report: Youth Self-Report Scale (Achenbach & Edelbrock, 1983) or Young Adult Self-Report Scale (Achenbach, 1997) or Adult Self Report Scale (Achenbach and Rescorla, 2003)
Childhood Gender Identity and Gender Role Behaviors	Recalled Childhood Gender Identity/Gender Role Questionnaire (Zucker et al., 2006)
Current Gender Identity and Gender Role Behaviors	<i>Self Report :</i> 1) Gender Identity Questionnaire for Adolescents and Adults (Deogracias et al., 2005; Singh et al., 2010) or Gender Dysphoria Questionnaire (Zucker et al., 1996) 2) Semi-structured interview for Gender Identity Disorder (Appendix G) <i>Parent Report:</i> 3) Gender Identity/Gender Role Questionnaire for Adolescents (Zucker, Bradley, Owen-Anderson, & Singh, 2010)
Sexual Orientation in Fantasy (past 12 months)	Kinsey Ratings (Kinsey et al., 1948) Erotic Response and Orientation Scale (Storms, 1980)
Sexual Orientation in Behavior (past 12 months)	Kinsey Ratings (Kinsey et al., 1948) Sexual History Questionnaire (Langevin, 1985)
Social Desirability	Marlowe-Crowne Social Desirability Scale (Crowne & Marlowe, 1960)
Victimization Experiences	Victimization Survey (Drummond, 2006)
Suicidality	Suicidality Questionnaire (Drummond, 2006)

Note. WAIS-III = Wechsler Adult Intelligence Scale-Third Edition; WAIS-IV = Wechsler Adult Intelligence Scale-Fourth Edition; WISC-III = Wechsler Intelligence Scale for Children-Third Edition; WISC-IV = Wechsler Intelligence Scale for Children-Fourth Edition.

Wechsler, 1997) or the Wechsler Adult Intelligence Scale-Fourth Edition ($n = 32$; WAIS-IV; Wechsler, 2008). Participants under the age of 17 were administered either the Wechsler Intelligence Scale for Children-Revised ($n = 25$; WISC-R; Wechsler, 1974), the Wechsler Intelligence Scale for Children-Third Edition ($n = 16$; WISC-III; Wechsler, 1991), or the Wechsler Intelligence Scale for Children-Fourth Edition ($n = 12$; WISC-IV, Wechsler, 2003).

2.3.2.2 Behavioral Functioning

For participants younger than 19 years, the Youth Self-Report (YSR; Achenbach, 1991) was used to assess behavior and emotional problems. For participants 19 years and older, the Young Adult Self-Report (YASR; Achenbach, 1997) or the Adult Self-Report (ASR; Achenbach & Rescorla, 2003) was used. *T* scores for Internalizing, Externalizing, and Total Behavior Problems were derived for each participant. The YSR is a 103 item self-report questionnaire that assesses emotional and behavior problems for ages 11 to 18 years. The YASR, the predecessor of the Adult Self-Report, contains 119 items to measure psychopathology in individuals 18 to 30 years. The YASR was utilized in data collection until the ASR was published. The ASR contains 126 items to measure psychopathology for individuals aged 18 to 59 years. The YSR, YASR, and ASR are variations of the CBCL and have the same 3-point format (0 = not true, 1 = sometimes true or somewhat true, 2 = very true or often true). The YSR has been reported to have good reliability and validity for identifying adolescent behavior problems (Achenbach, 1997). Several studies have used these scales to examine the course and predictive value of self-reported problems among adolescents and adults (Hofstra, van der Ende, & Verhulst, 2000, 2001).

Although assessment of adult psychopathology relies extensively on self-report, meta-analyses of studies comparing self-report and an informant's report revealed moderate

correlations between cross-informant data for substance abuse, internalizing, and externalizing problems (Achenbach, Krukowski, Dumenci, & Ivanaova, 2005). Participants gave permission to have their parent/guardian or spouse/partner complete the Child Behavior Checklist (CBCL; Achenbach, 1991) for those participants less than 18 years or the Adult Behavior Checklist (ABCL; Achenbach & Rescorla, 2003) for participants 18 years or older. Forms were given to those parents or guardians that came to the clinic with the participant or sent by mail to those that did not accompany the participant. *T* scores for Internalizing, Externalizing, and Total Behavior Problems were derived from the informant forms. Of the 110 participants who completed the follow-up assessment, parent report data were missing for 16 participants, either because the adult participants did not give consent to have their parents complete questionnaires or the parents did not return the questionnaires.

2.3.2.3 Psychiatric Functioning

Selected modules of the Diagnostic Interview for Children and Adolescents (DICA; Herjanic & Reich, 1982) or the Diagnostic Interview Schedule (DIS, Version IIIA; Robins, Helzer, Croughan, & Ratcliffe, 1981) were administered depending on age at follow-up. Participants younger than 18 were administered the DICA ($n = 64$) and those 18 years or older were administered the DIS ($n = 44$). Psychiatric data were not available for two of the 110 participants who completed the face-to-face assessment.

The DICA is a semi-structured psychiatric interview for youth between 6 and 17 years to assess the presence or absence of psychiatric diagnoses based on the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III, American Psychiatric Association, 1980). The DICA was patterned after the DIS. Ten DICA modules were included in this study: (1) Oppositional Disorder, (2) Conduct Disorder (Aggressive and

Non-aggressive), (3) Alcohol Abuse and Alcohol Dependence, (4) Major Depression, (5) Adjustment Disorder with Depressed Mood, (6) Mania, (7) Separation Anxiety, (8) Overanxious Disorder, (9) Marijuana Abuse, and (10) Other Drug Abuse and Drug Dependence. The total number of possible diagnoses a participant could meet criteria for on this measure was 13. The DICA has been demonstrated to have good reliability (Werner et al., 1987) and adequate validity (Carlson et al. 1987; Ezpeleta et al., 1997).

The DIS is a standardized structured interview devised to assess the presence or absence of psychiatric diagnoses in adults based on the DSM-III (American Psychiatric Association, 1980). Fourteen modules were included in this study: (1) Depression (Major Depression [single episode], Major Depression [recurrent], Grief Reaction), (2) Dysthymic Disorder, (3) Obsessive-Compulsive Disorder, (4) Agoraphobia, (5) Social Phobia, (6) Simple Phobia, (7) Panic Disorder, (8) Agoraphobia with Panic Attacks, (9) Generalized Anxiety Disorder, (10) Alcohol Abuse and Alcohol Dependence, (11) Drug Abuse and Drug Dependence, (12) Anorexia Nervosa and Bulimia, (13) Schizophrenia, and (14) Bipolar Disorder. The total number of possible diagnoses a participant could meet criteria for on this measure was 17. The DIS has been found to have excellent inter-rater reliability (Anduaga, Forteza, & Lira, 1991; Hesselbrock et al., 1982). There have been some concerns about the validity of the DIS (e.g., Helzer et al., 1985) as studies have yielded mixed results with kappas ranging from low to moderate (for review, see Rogers, 2001). Following the publication of the DSM-IV, the Diagnostic Interview Schedule for DSM-IV (DIS-IV) was published (Robins, Cottler, Bucholz, & Compton, 1995) to correspond to the updated DSM diagnostic criteria. Test-retest reliability and validity of the DIS-IV was assessed in a sample of drug users (Dascalu, Compton, Horton, & Cottler, 2001; Horton, Compton, & Cotter,

1998). Test-retest reliability and validity ranged from excellent to fair for most disorders. However, test-retest reliability was considered poor for generalized anxiety disorder and specific phobia, kappa = .35 and .25, respectively (for more details on specific diagnoses, see Compton & Cottler, 2004).

For the DIS and the DICA, the total number of diagnoses each participant met criteria for was calculated.

2.3.2.4 Psychosexual Variables

The present study examined seven self-report measures of psychosexual outcome and one parent-report measure pertaining to sex-typed behavior.

2.3.2.4.1 Recalled Childhood Gender Identity and Gender Role Behaviors

Participants completed the Recalled Childhood Gender Identity/Gender Role Questionnaire (Zucker et al., 2006). This questionnaire consists of 23 items pertaining to various aspects of childhood sex-typed behavior and identification (e.g., peer preferences, toy preferences, roles in fantasy play, and feelings about being a male as a child), as well as relative closeness to mother and father during childhood. Items were rated on a 4-point or 5-point scale. For some items, however, an additional response option allowed the participant to indicate that the behavior did not apply (e.g., for the question about favorite playmates, there was the option “I did not play with other children”). Each participant was instructed to make ratings for their behavior as a child (“between the years 0 to 12”). Factor analysis identified two factors, accounting for 37.4% and 7.8% of the variance, respectively (all factor loadings $\geq .40$). Factor 1 consisted of 18 items that pertained to childhood gender role and gender identity and Factor 2 consisted of three items that pertained to parent-child relations (relative closeness to one’s mother vs. father). Significant variation in factor scores between

groups completing the RCGI was reported (e.g., heterosexual versus homosexual adults, adolescents with GID versus transvestic fetishism, women with CAH versus their sisters or female cousins), demonstrating that the questionnaire has good discriminant validity (Singh et al., 2010; Zucker et al., 1996a, 2006). For the present study, this questionnaire was used as a measure of recalled gender role and gender identity behaviors and, as such, the mean Factor 1 score was computed for each participant. Lower scores represent more recalled childhood cross-gender behaviors. The RCGI was added to the assessment protocol in 1993, after data collection had begun, so some data were missing for individuals who completed the follow-up prior to the inclusion of this measure.

2.3.2.4.2 Concurrent Gender Identity

Concurrent gender identity was evaluated using interview and self-report data. During an audiotaped interview, each participant was asked to describe their current feelings about being a biological male. They were also asked to describe positive and negative aspects about their gender identity. For example, participants who reported a “male” gender identity were asked to describe positive and negative aspects of being male. Participants were also administered a semi-structured gender identity interview (see Appendix G) based on the adolescent and adult GID criteria outlined in the DSM-IV-TR (American Psychiatric Association, 2000). The interview contained five questions related to the Point A criteria (e.g., the stated desire to be a woman, passing as a woman, the desire to live or be treated as a woman) and four questions from the Point B criteria (e.g., a preoccupation with getting rid of their penis, belief that they should have been born a woman). Participants were asked to respond to these questions according to the last 12 months with *No*, *Sometimes*, or *Yes*.

Two self-report measures were also used to assess current gender identity and gender dysphoria: (a) The Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults (GIQAA; Deogracias et al., 2007; Singh et al., 2010), or (b) the Gender Dysphoria Questionnaire (GDQ; Zucker et al., 1996a). The GDQ was developed prior to the GIQAA. As such, the GIQAA was introduced to the clinical battery subsequent to the GDQ and, as a result, the more recent participants were administered the GIQAA while earlier participants were given the GDQ. The GIQAA and GDQ differ in number of items and rating scale. They also differ in the wording of questions. In order to integrate the data collected from the GIQAA and GDQ, participants' score on each measure was converted to a proportion score which ranged from 0-1. The proportion score, referred to hereafter as the gender dysphoria score, was used in all analyses instead of the mean scores on the GIQAA and GDQ. The gender dysphoria score reflects the proportion of the highest possible score that each participant received on either the GIQAA or the GDQ. For example, a participant with a proportion score of 1.00 on either the GIQAA or GDQ received the maximum score on that measure. A higher proportion score indicates more gender dysphoria. There were, however, some participants who completed the GIQAA and the GDQ ($n = 17$). In these cases, the GIQAA proportion score was used as it is a more psychometrically sophisticated measure of gender dysphoria compared to the GDQ.

The male version of the GIQAA (Deogracias et al., 2007; Singh et al., 2010) was completed. This 27-item questionnaire measures gender identity and gender dysphoria in adolescents or adults; participants over the age of 17 completed the adult version and younger participants completed the adolescent version. The adolescent and adult versions are identical in all regards except that, in the adult version, the words "man" and "woman" are

used instead of “boy” and “girl.” The items were developed by the North American Task Force on Intersexuality (NATFI) Research Protocol Working Group (S. J. Kessler, H. F. L. Meyer-Bahlburg, J. M. Schober, and K. J. Zucker) based on prior measures, expert panels, and clinical experience, and were designed to capture multiple indicators of gender identity and gender dysphoria, including subjective (n = 13 items), social (n = 9 items), somatic (n = 3 items), and sociolegal (n = 2 items) parameters. Each item was rated on a 5-point response scale from *Never* (coded as 1) to *Always* (coded as 5) based on a time frame of the past 12 months. Item examples include the following: “In the past 12 months, have you felt unhappy about being a man?” and “In the past 12 months, have you had the wish or desire to be a woman?” Principal axis factor analysis identified a one-factor solution that accounted for 61.3% of the variance. All factor loadings were $\geq .30$ (median, .86; range, .34-.96). The GIQAA demonstrated evidence for discriminant validity and a high threshold for specificity (i.e., low false positive rate for non-GID individuals).

In a replication and extension of this study, Singh et al. (2010) compared adults and adolescents with GID to clinical controls (i.e., evaluated for reasons other than GID or transvestic fetishism). There was strong evidence for discriminant and convergent validity, with high sensitivity and specificity rates. Males and females with GID reported significantly more gender dysphoria than clinical controls, with large effect sizes (Cohen, 1988). Deogracias et al. (2007) suggested that the mean score on the Gender Identity Questionnaire for Adolescents and Adults (GIQAA) can be used to determine whether a participant was gender dysphoric, and, in their sample, used a mean score of ≤ 3 ¹⁸ to indicate a “case” of gender dysphoria. Using this criterion for caseness, the measure was able to identify gender

¹⁸ Absolute range on the GIQAA is 1-5, with a lower score reflecting more gender dysphoria.

dysphoric adolescents with 93.3% sensitivity. For the clinical control participants, specificity (i.e., low false positive rate for non-GID individuals) was 100% (i.e., none of the clinical control participants met criteria for caseness). For adults, sensitivity was 87.8% for the GID participants and specificity was 100% for the clinical controls. In a subsequent study, Singh, McMain, and Zucker (2011) administered the GIQAA to 100 women diagnosed with borderline personality disorder (BPD), none of whom were ever evaluated in a gender clinic. Using the suggested GIQAA mean score of 3 as the cut-off for identifying gender dysphoria, none of the women with BPD met this criterion for caseness. Zucker et al. (2010) reported on 105 adolescent males with GID, of whom, 91.7% met criterion for caseness. Additional psychometric evidence for discriminant validity and clinical utility can also be found in Singh et al. (2011).

The Gender Dysphoria Questionnaire (Zucker et al., 1996a) contains 8 items pertaining to gender identity and gender dysphoria. Each item was rated on a 3-point or 5-point scale based on a time frame of the past 6 months. Item examples include the following: “In the past 6 months, how often have you wished that you had been a born a girl instead of a boy?” (with response options ranging from “never” to “a lot”) and “In the past 6 months, how have you felt about being a boy?” (with response options ranging from “very satisfied” to “very dissatisfied”). Factor analysis identified two factors, accounting for 31.4% and 12.5% of the variance, respectively (all factor loadings $\geq .45$). Factor 1 consisted of 5 items pertaining to gender dysphoria and Factor 2 consisted of 3 items pertaining to gender role identification. For the present study, the mean Factor 1 score was computed for each participant.

Using the questionnaire data on concurrent gender identity, participants were classified as either gender dysphoric (“persisters”) or not gender dysphoric (“desisters”) at follow-up. The Results section outlines the specific criteria used to make this classification.

2.3.2.4.3 Concurrent Gender Role–Parent Report

The *Gender Identity/Gender Role Questionnaire for Adolescents (GIGRQ-Ad)* is a 13-item parent-report questionnaire pertaining to various aspects of concurrent sex-typed behavior (e.g., sex-of-peer affiliation preference, masculine vs. feminine interests, cross-dressing, the desire to be of the other sex; Zucker, Bradley, Owen-Anderson, & Singh, 2010b). Items were rated on a 5-point response scale, with the exception of a Peer Composite item, in which a difference score between the number of male and female friends was calculated. Factor analysis of the GIGRQ-Ad was based on a sample of 403 youth, including various comparison groups, such as siblings and clinical controls. A principal axis factor analysis identified a one-factor solution, accounting for 44.8% of the variance. Ten of the 14 items had factor loadings $\geq .43$ (range, .43-.82) and, for these items, a unit-weighted mean total score was derived. Cronbach’s alpha for this measure was .91. A lower score indicates more cross-gender behavior. Discriminant validity was reported in Zucker et al. (2010b).

2.3.2.4.4 Sexual Orientation

As stated previously, in sexology research sexual orientation is often measured using two metrics: sexual orientation in fantasy and sexual orientation in (overt) behavior (Green, 1987). For the present study, participants’ sexual orientation in fantasy and behavior was assessed using a multi-method approach: face-to-face interview and self-report. Participants’ sexual orientation was classified in relation to their biological (birth) sex.

2.3.2.4.4.1 Sexual Orientation in Fantasy

Each participant's sexual orientation in fantasy was assessed with specific questions from an audiotaped face-to-face interview and the self-report Erotic Response and Orientation Scale (EROS; Storms, 1980).

Questions posed in the audiotaped interview asked about four types of sexual fantasy: (1) crushes on other people; (2) sexual arousal to visual stimuli (e.g., strangers, acquaintances, partners, and individuals presented in the media [video, movies, magazines, internet]; (3) sexual content of night dreams; and (4) sexual content of masturbation fantasies. During the interview, participants were not asked directly about the gender of the person or persons who elicited sexual arousal, thus allowing time for the participant to provide this information spontaneously. Directed questions about the gender of the person(s) who elicited sexual arousal were asked only if the participant did not volunteer specific information about whether their arousal was directed to same-sex or opposite-sex partners, or both. By the end of the interview, each participant provided information about sexual arousal to both same-sex and opposite-sex individuals. Using the Kinsey scale criteria (Kinsey, Pomeroy, & Martin, 1948), the interviewer assigned Kinsey ratings that ranged from 0 (exclusively heterosexual in fantasy) to 6 (exclusively homosexual in fantasy) for each question.¹⁹ A dummy score of 7 denoted that the participant did not experience or report any fantasies. A global fantasy score was also derived based on ratings from the four questions. In the present study, only ratings for the last 12 months are reported since one goal of the study was to assess sexual orientation at the time of follow-up. During the interview,

¹⁹ The Kinsey Scale: 0 = Exclusively heterosexual, 1 = Predominantly heterosexual, only incidentally homosexual 2 = Predominantly heterosexual but more than incidentally homosexual, 3 = Equally homosexual and heterosexual, 4 = Predominantly homosexual, but more than incidentally heterosexual, 5 = Predominantly homosexual, but incidentally heterosexual, and 6 = Exclusively homosexual (Kinsey et al. 1948).

however, participants were asked about their “lifetime” (i.e., from age 13 until present) history of sexual fantasies. Kinsey ratings for sexual orientation in fantasy were available for 129 participants.

Inter-rater reliability on Kinsey ratings for sexual orientation in fantasy was examined for 29 participants, which were selected at random. The second scorer listened to the audio recordings of the semi-structured interview, with specific attention to the information collected on sexual orientation. The second coder was masked to participants’ group status at follow-up. The inter-rater agreement on the Kinsey Global Fantasy rating was very good ($kappa = .95$). For reference purposes, Appendix H lists the inter-rater agreement for each type of sexual fantasy evaluated during the semi-structured interview.

The Erotic Response and Orientation Scale (EROS) is a 16-item self-report measure assessing sexual orientation in fantasy over the past 12 months. Half of the questions pertained to heterosexual fantasy (e.g., “How often have you noticed you had sexual feelings (even the slightest) while looking at a woman?”) and the other half pertained to homosexual fantasy (e.g., “How often have you noticed you had sexual feelings (even the slightest) while looking at a man?”). Each item was rated on a 5-point scale for frequency of occurrence, ranging from “none” to “almost every day.” Mean homoerotic and heteroerotic fantasy scores were derived for each participant. Previous use of the EROS has shown good evidence of discriminant validity, such that it is able to discriminate between responses of self-identified heterosexual and homosexual men and women (Storms, 1980; Zucker et al., 1996a).

2.3.2.4.4.2 Sexual Orientation in Behavior

Each participant’s sexual orientation in behavior was assessed with specific questions

during the face-to-face interview and with a modified version of the Sexual History Questionnaire (SHQ; Langevin, 1985).

In the interview, questions asked about five types of sexual behavior: (a) dating; (b) holding hands in a romantic manner; (c) kissing; (d) genital fondling or touching a woman on the breasts, and (e) intercourse (penile-vaginal and anal). Kinsey ratings for behavior in the past 12 months were made in the same manner as fantasy ratings.

Inter-rater reliability on Kinsey ratings for sexual orientation in behavior was examined for 29 participants, which were selected at random. The second scorer listened to the audio recordings of the semi-structured interview, with specific attention to the information collected on sexual orientation. The second coder was masked to participants' group status at follow-up. There was perfect inter-rater agreement on the Kinsey Global Behavior rating ($kappa = 1.0$). For reference purposes, Appendix H lists the inter-rater agreement for each type of sexual behavior evaluated during the semi-structured interview.

The modified Sexual History Questionnaire (SHQ) consists of 20 questions. Ten questions pertained to heterosexual experiences (e.g., "How many women have you kissed on the lips in a romantic way?") and 10 questions pertained to homosexual experiences (e.g., "How many men have you kissed on the lips in a romantic way?"). Participants who were 18 years and older completed the adult version and younger participants completed the adolescent version. The adolescent and adult versions are similar in all regard except that, in the adult version, the words "man" and "woman" are used instead of "boy" and "girl." Each item was rated on a 5-point scale for frequency of occurrence, ranging from none to 11 or more, based on a time frame of the past 12 months. Mean total scores for heterosexual and homosexual experiences were derived.

2.3.2.4.4.3 Sexual Orientation Group Classification

On the basis of Kinsey ratings, participants who completed the face-to-face interview were classified into the following three sexual orientation groups for both fantasy and behavior: (1) heterosexual (Kinsey global ratings of 0-1); (2) bisexual/homosexual (Kinsey global ratings of 2-6), and (3) no sexual fantasy or behavior. Participants' sexual orientation was classified in relation to their birth sex.

A comment is warranted on the decision to combine the bisexual and homosexual participants. This validity of this procedure has been questioned (e.g., MacDonald, 1983; Paul, 1993) on the basis that combining bisexuals with homosexuals in research samples, though standard among sex researchers, confounds the research on both groups. In the present study, and similar to Green's (1987) follow-up study, participants who were categorized as bisexual or homosexual on the basis of their Kinsey ratings were combined for a number of reasons. On the basis of extensive clinical experience, Zucker and Bradley (1995) stated that it is common for homosexual men to recall a period of bisexual behavior during adolescence. It is, therefore, conceivable that some adolescent participants who reported bisexual behavior and/or fantasies will move toward an exclusively homosexual sexual orientation in adulthood. Research on sexual identity development has demonstrated that men who adopt a homosexual identity might go through a stage in which they identify as bisexual (e.g., Lever, 1994; Stokes, Damon, & McKirnan, 1997). Recent research on the sexual arousal patterns of men who identify as bisexual has found that most were more strongly aroused by homosexual stimuli than by heterosexual stimuli and, therefore, appear to be homosexual with respect to their genital arousal (Rieger, Chivers, & Bailey, 2005). Moreover, decades of research on "coming out" as gay or homosexual has shown that the

period of first disclosure can range from during mid-adolescence, around 16 or 17 years of age (e.g., D'Augelli, Hershberger, & Pilkington, 1998; Grov, Bimbi, Nanin, & Parson, 2006) to late adolescence and early 20s (e.g., McDonald, 1982; Savin-Williams, 1998; Savin-Williams & Ream, 2003) and depends on numerous factors, including ethnicity, relationship with parents and their anticipated reaction, and person to whom the individual is disclosing—individuals with same-sex attractions typically come out to a supportive friend before coming out to parents (Beaty, 1999; Savin-Williams & Dube, 1998). Finally, it was not a goal of the present study to embark on a comparison of exclusively homosexual versus bisexual participants.

2.3.2.5 Social Desirability

Social desirability refers to the desire to cast a favorable impression on others. It can threaten the validity of self-report scales if in answering questions respondents seek social approval or try to represent themselves in a favorable manner (King & Brunner, 2000; Tan & Grace, 2008). People scoring high on social desirability tend to provide socially acceptable answers regardless if their response accurately describes them. As such, researchers have recognized that, particularly when assessing attributes of a personal or sensitive nature, such as an individual's sexual history, the respondents' propensity to give socially desirable responses should be measured (e.g., Wallien & Cohen-Kettenis, 2008). Participants 18 years and older were given the Marlow-Crowne Social Desirability Scale (M-CSDS; Crowne & Marlowe, 1960), which consists of 33 true-false items. The scale consists of 18 culturally acceptable but unlikely statements keyed in the true direction and 15 socially undesirable but probable statements keyed in the false direction for a maximum possible score of 33. Participants 17 years and under, were given a shorter version of the M-CSDS (Strahan &

Gerbasi, 1972), containing 20 items that consists of 12 culturally acceptable but improbable statements keyed in the true direction and 8 socially undesirable but probable statements keyed in the false direction for a maximum possible score of 20. For the present study, the percentage of endorsed socially desirable items was calculated for each participant. In order to integrate the data from both versions of the M-CSDS, participants' percentage score on each measure was converted to a proportion score which ranged from 0-1, which was used in all analyses. A higher proportion score indicates a greater propensity to give socially desirable responses. Several studies have found that the MCSDS is a reliable and valid measure of social desirability (Crowne & Marlowe, 1960; Holden & Feeken, 1989; Silverthorn & Gekoski, 1995).

2.3.2.6 Suicidality Experiences

Suicidal experiences were assessed with a Suicidality Questionnaire (see Appendix I) that consists of 13 items derived from Centre for Disease Control and Prevention Survey on Youth Risk Behavior Surveillance System (Brener et al., 2002; CDC, 2002) and questionnaires given in other studies (D'Augelli et al., 2002; Savin-Williams & Ream, 2003). Six of the questions pertained to "lifetime" experiences (since the age of 13) and 7 pertain to suicidal thoughts and/or experiences within the past 12 months. Frequencies of suicidality experiences were derived. Participants' responses on this questionnaire were reviewed before they left the clinic. A procedure was set in place such that participants who expressed suicidal thoughts would be asked additional questions as part of a risk assessment; however, none of the study participants were at imminent risk for suicide. The Suicidality Questionnaire was introduced to the study protocol after data collection had begun; therefore, some participants did not complete this measure. In these instances, data on suicidality were

extracted from their psychiatric interview (i.e., the Diagnostic Interview Schedule or the Diagnostic Interview for Children and Adolescents).

2.3.2.7 Victimization Experiences

Victimization experiences were assessed through a 12-item Victimization Survey (see Appendix J), which was adapted from previous studies on sexual orientation victimization of lesbian and gay youth and adults (D'Augelli et al., 2002; D'Augelli & Grossman, 2001; Herek, Gillis, Cogan, & Glunt, 1997). The survey was modified to target victimization due to cross-gender behavior. Questions ask participants' frequency of victimization experiences over the past 12 months and since the age of 13 (i.e., "lifetime" victimization experiences). Seven types of victimization experiences were asked, including three verbal and four physical types. Verbal victimization included: (a) verbal insults, (b) threats of violence, and (c) threats by other to disclose gender identity. Physical victimization consisted of: (a) objects being thrown at the individual, (b) physical assault (e.g., being punched, kicked, or beaten), (c) threat of an attack, using a knife, gun, or weapon, and (d) sexual assault. Participants responded to each question based on the frequency of occurrence for each type of victimization with 0 = "Never," 1 = "Once," 2 = "Twice," and 3 = "Three or more times." An average verbal victimization score, an average physical victimization score, and an average total victimization score was computed (the sum of all items divided by the relevant number of items) for ratings based on lifetime experiences as well as the past 12 months (D'Augelli, Pilkington, & Hershberger, 2002). Participants were also asked about the location of their victimization experiences (e.g., home, school, neighborhood, work place) and the type of relationship they had with the assaulter (e.g., parent, sibling, significant other, peer, or stranger). The Victimization Survey was added to the assessment protocol in 2008,

after data collection had begun, so data were missing for individuals who completed the follow-up prior to the inclusion of this measure.

Chapter 3

Results

3.1 Participants vs. Non-Participants

The non-participants represent three groups: (1) patients who were eligible to participate in the study but were not contacted ($n = 163$), (2) patients who declined to participate in the study ($n = 6$), and (3) patients who were not successfully traced ($n = 19$). Two sets of analyses were conducted to compare the study participants with the non-participants. First, the study participants were compared to the boys who were eligible but were not contacted for research follow-up. Second, the study participants were compared to those who refused to participate in the study and to those where contact was attempted but the families were not successfully traced. Group comparisons were conducted on demographic variables (age at assessment, IQ, social class, marital status, ethnicity), CBCL behavior problems (Internalizing T score, Externalizing T score, Total T score), and nine measures of childhood sex-typed behavior.

Table 5 shows the childhood assessment data (demographics and CBCL behavior problem ratings) of the 139 boys who participated in the study compared to the 163 boys who were eligible to participate but were not contacted due to time constraints and lack of study resources. There were no significant differences between the participants and non-participants on the demographic variables of age at assessment, social class, ethnicity or marital status ($ps > .05$). However, the comparison on childhood IQ was significant, $t(289)^{20} = 2.01, p = .046$, with the participants having a higher IQ than the non-participants. The effect size for this comparison was small (unpooled $d = .22$). With regard to parent-report of behavior problems on the CBCL, there were no significant differences between the

²⁰ IQ data were missing for 11 of the 163 boys who were eligible for the study but were not contacted.

Table 5
Demographic Characteristics and Behavior Problems as a Function of Participant Status

	Participants (<i>n</i> = 139)	Non-Participants ^a (<i>n</i> = 163)	χ^2	<i>p</i>		
Demographic Characteristics						
Marital Status of Parents						
Two-Parent	90 (64.7)	109 (66.9)	<1	ns		
Other ^b	49 (35.3)	54 (33.1)				
Ethnicity						
Caucasian	118 (84.9)	136 (83.4)	<1	ns		
Non-Caucasian	21 (15.1)	27 (16.6)				
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>t</i>	<i>p</i>
Age at Assessment	7.49	2.66	7.03	2.30	1.59	ns
Social Class	40.74	15.15	43.05	14.48	-1.35	ns
IQ ^c	105.93	15.47	102.11	16.88	2.01	.046
Behavioral Problems						
Internalizing <i>T</i> Score	62.20	9.86	62.19	11.35	<1	ns
Externalizing <i>T</i> Score	60.86	10.93	61.29	12.14	<1	ns
Total <i>T</i> Score	62.77	11.38	62.70	12.79	<1	ns

^aBoys who were eligible to participate but were not contacted.

^b“Other” includes single parent, separated, divorced, living with relatives.

^cAge appropriate version of the Wechsler Intelligence Scale was administered.

participants and non-participants on Internalizing problems, Externalizing problems, and Total problems ($ps > .05$). The participants and non-participants were also compared on their diagnosis in childhood and their scores on measures of sex-typed behavior (Table 6). There was no significant difference between the participants and non-participants in terms of whether they were diagnosed with GID in childhood or were subthreshold for the diagnosis, $\chi^2(1) < 1$. There were also no significant differences between the participants and non-participants on any of the eight measures of sex-typed behavior ($ps > .05$). In sum, of the 17 analyses conducted to examine the differences between the participants and those who were eligible to participate but were not contacted, only one comparison (childhood IQ) was

Table 6

Childhood Sex-Typed Behavior as a Function of Participant Status

	Participants (<i>n</i> = 139)			Non-Participants (<i>n</i> = 163)				
	N	%	N	%	χ^2	<i>p</i>		
DSM Diagnosis ^a	N (%)							
Threshold for GID	88	63.3	105	64.4	<1	ns		
Subthreshold for GID	51	36.7	58	35.6				
Draw-a-Person								
Same-Sex	63	45.7	67	44.7	<1	ns		
Cross-Sex	75	54.3	83	55.3				
	<i>M</i>	<i>SD</i>	N	<i>M</i>	<i>SD</i>	N	<i>t</i>	<i>p</i>
Child measures								
Free Play Task ^b	.11	.64	121	.09	.58	146	<1	ns
Rorschach Difference Score ^c	.57	3.74	125	.72	3.83	78	<1	ns
Gender Identity Interview ^d	6.31	5.82	85	6.03	5.52	145	<1	ns
Playmate and Playstyle Preferences Structured Interview: Cross-sex peer play ^e	8.44	5.37	41	8.48	5.23	108	<1	ns
Playmate and Playstyle Preferences Structured Interview: Cross-sex toy play ^f	7.07	2.99	41	6.90	2.97	108	<1	ns
Parent measures								
Gender Identity Questionnaire for Children ^g	2.86	.66	97	2.90	.59	149	<1	ns
Temperament: Activity Level ^h	3.05	.53	136	3.09	.61	151	<1	ns

^aFor diagnosis, GID means that the patient met complete DSM-III, DSM-III-R, or DSM-IV criteria for GID.

^bDifference between cross-sex and same-sex play during a free-play task. Positive score indicates more cross-sex play.

^cDifference between number of same-sex and cross-sex responses. Positive score indicates more cross-sex responses.

^dAbsolute range, 0-24. A higher score reflects more gender identity confusion.

^eAbsolute range, 0-14. A higher score indicates more cross-sex playmate/peer choices.

^fAbsolute range, 0-14. A higher score indicates more cross-sex toy choices.

^gAbsolute range, 1-5. A lower score indicates more cross-gender behavior.

^hHigher ratings indicate elevated activity levels and more rough-and-tumble play.

significant.

Using one-way ANOVA or chi-square, the study participants were also compared to the 6 cases where either the parents or the potential participant himself refused to participate and to the 19 cases where the families could not be traced. Group comparisons were conducted on demographic variables, CBCL behavior problems, and measure of sex-typed behavior. There were no significant group differences on the demographic variables of age, social class, and ethnicity ($ps > .05$). The ANOVA on childhood IQ approached significance, $F(2, 162) = 2.99, p = .053$. Duncan's multiple range test for unequal Ns showed that the participants did not differ significantly from the other two groups; however, the non-participants who refused had a higher IQ in childhood than those who could not be traced. The three groups differed significantly on marital status, $\chi^2(2, N = 164) = 9.02, p = .011$. Post-hoc analyses were done using chi-square or Fisher's Exact Test. The participants did not differ significantly from the non-participants who refused; however, they differed significantly from the cases that could not be traced, $\chi^2(1, N = 158) = 6.39, p = .012$. The participants were more likely to have originated within a two-parent household while those who could not be traced were more likely to have come from a family composition other than two-parent (e.g., single parent, living with relatives). The comparison between the non-participants who refused and those who could not be traced approached significance ($p = .056$, Fisher's exact test). Again, the non-participants who could not be traced were more likely to have come from a family composition that was not two-parent. With regard to parent-report of behavior problems on the CBCL, there were no significant differences between the three groups on Internalizing problems, Externalizing problems, and Total problems ($ps > .05$). The three groups were also compared on their diagnosis in childhood

and on measures of sex-typed behavior. There was no significant difference between the three groups on their diagnosis in childhood; the participants were as likely to have met full diagnostic criteria for GID as the non-participants. There were also no significant group differences on any of the measures of sex-typed behavior ($ps > .05$). In sum, of the 17 analyses conducted to compare the participants to those who refused and to those who could not be traced, one (marital status) was significant and one (childhood IQ) approached significance. The other 15 group comparisons were not significant.

3.2 DSM Diagnosis for Gender Identity Disorder in Childhood

Of the 139 participants, 88 (63.3%) met diagnostic criteria for GID in childhood and the remaining 51 (36.7%) were subthreshold for the diagnosis. These two groups were compared on demographic variables, CBCL behavior problems, and measures of sex-typed behavior. There were no significant group differences on the demographic variables of IQ in childhood, marital status or ethnicity ($ps > .05$). However, the threshold participants were significantly younger in age at the time of the childhood assessment, $t(108) = -6.31, p < .001$, and originated within a family of higher social status compared to the subthreshold participants, $t(108) = 2.31, p = .023$. The effect size for these differences was medium, .34 and .46, respectively.

3.2.1 Childhood Behavior Problems as a Function of Diagnostic Status for Gender Identity Disorder

One-way ANCOVAs, with age and social class covaried, were conducted to evaluate whether the two diagnostic groups differed on CBCL behavior problems and sex-typed behavior in childhood. There were no significant differences between the threshold and subthreshold participants on Internalizing T score and Total T score (both $ps > .05$). The

subthreshold participants were rated by their parents as having, on average, significantly more externalizing difficulties ($M = 61.02$, $SD = 11.78$) compared to the threshold participants ($M = 60.77$, $SD = 10.48$), $F(1, 138) = 7.86$, $p = .006$, partial $\eta^2 = .06$. Visual inspection revealed modest differences in Externalizing T scores between the two groups.

3.2.2 Childhood Sex-Typed Behavior as a Function of Diagnostic Status for Gender Identity Disorder

Table 7 shows the means and SD s (for continuous variables) or percentage scores (for dichotomous variables) for the threshold and subthreshold participants on measures of childhood sex-typed behavior. With age and social class covaried, the threshold participants had, on average, more cross-gender behavior in childhood than did the subthreshold participants. There were significant group differences on five of eight measures of childhood sex-typed behavior: (1) the Draw-a-Person test ($p < .001$), (2) free play, $F(1, 120) = 28.94$, $p < .001$, partial $\eta^2 = .19$, (3) Gender Identity Interview, $F(1, 84) = 9.07$, $p < .001$, partial $\eta^2 = .10$, (4) Gender Identity Questionnaire for Children, $F(1, 96) = 19.13$, $p < .001$, partial $\eta^2 = .17$ and (5) cross-sex toy choice on the Playmate and Play Style Preferences Structured Interview, $F(1, 40) = 9.72$, $p = .004$, partial $\eta^2 = .21$. The groups did not differ on temperament/activity level, cross-sex peer preference on the Playmate and Play Style Preferences Structured Interview, and difference between cross-sex and same-sex responses on the Rorschach ($ps > .05$).

3.3 Psychosexual Differentiation

3.3.1 Gender Identity at Follow-up

A summary of the psychosexual differentiation follow-up data, including gender identity and sexual orientation for each participant is shown in Appendix K.

Table 7

Childhood Sex-Typed Behavior as a Function of Diagnostic Status for Gender Identity Disorder in Childhood

	Threshold ^a (<i>n</i> = 88)			Subthreshold (<i>n</i> = 51)				
	N	%		N	%		χ^2	<i>p</i>
Draw-a-Person								
Same-Sex	26	29.5		37	74.0		25.40	<.001
Cross-Sex	62	70.5		13	26.0			
	<i>M</i>	<i>SD</i>	N	<i>M</i>	<i>SD</i>	N	<i>F</i>	<i>p</i>
Child measures								
Free Play Task ^b	.33	.53	85	-.40	.55	36	28.94	<.001
Rorschach Difference Score ^c	.58	3.74	78	.55	3.71	47	<1	ns
Gender Identity Interview ^d	8.11	5.82	57	2.64	3.77	28	9.07	<.001
Gender Identity Questionnaire for Children ^e	2.65	.60	64	3.27	.58	33	19.13	<.001
Parent measures								
Playmate and Playstyle Preferences Structured Interview: Cross-sex peer play ^f	10.17	4.68	30	3.73	4.27	11	3.69	ns
Playmate and Playstyle Preferences Structured Interview: Cross-sex toy play ^g	8.03	2.72	30	4.45	2.02	11	9.72	.004
Temperament: Activity Level ^h	3.10	.49	88	2.95	.59	48	<1	ns

^aThreshold means that the patient met complete DSM-III, DSM-III-R, or DSM-IV criteria for GID.

^bDifference between cross-sex and same-sex play during a free-play task. Positive score indicates more cross-sex play.

^cDifference between number of same-sex and cross-sex responses. Positive score indicates more cross-sex responses.

^dAbsolute range, 0-24. A higher score reflects more gender identity confusion.

^eAbsolute range, 1-5. A lower score indicates more cross-gender behavior.

^fAbsolute range, 0-14. A higher score indicates more cross-sex playmate/peer choices.

^gAbsolute range, 0-14. A higher score indicates more cross-sex toy choices.

^hHigher ratings indicate elevated activity levels and more rough-and-tumble play.

3.3.1.1 Criteria for Persistence of Gender Dysphoria

Classification as either a persister or desister with regard to gender dysphoria was based on participants' mean scores on the dimensional measures of concurrent gender identity, either the Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults or the Gender Dysphoria Questionnaire, depending on which measure was administered. Some participants completed both measures and, in these cases, the Gender Identity/Gender Dysphoria Questionnaire for Adolescents data were used as the basis for classification as it is a more psychometrically sophisticated measure of gender dysphoria compared to the Gender Dysphoria Questionnaire.

Participants were classified as having persistent gender dysphoria if their mean score on the Gender Identity/Gender Dysphoria Questionnaire for Adolescents was ≤ 3.00 (Deogracias et al., 2007). For participants who did not complete the Gender Identity/Gender Dysphoria Questionnaire for Adolescents, the Gender Dysphoria Questionnaire was used to make the classification. A participant was classified as a persister if he endorsed two or more of the following 5 items on the Gender Dysphoria Questionnaire: wish to have been born a girl (Item 1), wish to have surgery to change body (Item 2), feel more like a girl than a boy (Item 3), wonder if would be happier as a girl (Item 4), and very or somewhat dissatisfied with being a boy (Item 5).

Information regarding participants' gender identity/gender dysphoria was also collected during the semi-structured clinical interview and, therefore, allowed for cross-validation of these questionnaire data. For those participants who did not complete the face-to-face interview, clinical information regarding gender identity/gender dysphoria was obtained through self- or parent-report or chart review. Across the entire sample, the Gender

Identity/Gender Dysphoria Questionnaire for Adolescents and Adults was used to classify persistence or desistence for 64 participants, the Gender Dysphoria Questionnaire for 42 participants, and interview/parent report/chart data for 33 cases.

3.3.1.2 Rate of Persistence and Desistence

Of the 139 participants, 17 (12.2%) were classified as persisters and the remaining 122 (87.8%) were classified as desisters at follow-up. For the 42 participants where the Gender Dysphoria Questionnaire was used to determine gender identity status at follow-up, 38 were classified as desisters and 4 were classified as persisters. Of the 38 desisters, three endorsed one item on the Gender Dysphoria Questionnaire –one participant endorsed Item 4 and two participants endorsed Item 3. The four participants classified as persisters using the Gender Dysphoria Questionnaire endorsed three or more items. Specifically, one persister endorsed three items, one endorsed four items, and two endorsed five items. In regard to the specific items endorsed, all four persisters endorsed Item 1, three endorsed Item 2, four endorsed Item 3, four endorsed Item 4, and two endorsed Item 5.

For the 64 participants where the Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults was used to determine gender identity status at follow-up, 12 were classified as persisters and the remaining 52 were classified as desisters. All 52 desisters had a mean score > 3.00 on the Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults. Of the 12 persisters, 10 had a mean score ≤ 3.00 and two had mean scores that were > 3.00 . In spite of having mean scores on the Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults that were above the recommended cutoff for caseness (Deogracias et al., 2007), these two participants were considered

persisters because their responses on the Gender Dysphoria Questionnaire as well as clinical interview data indicated that they were experiencing significant gender dysphoria. Thus, clinical judgment was used to make the final classification for these two participants.

3.3.1.3 Persistence of Gender Dysphoria as a Function of GID Diagnosis in Childhood

The persistence rate of gender dysphoria was examined as a function of participants' GID diagnostic status in childhood, that is, whether they met full diagnostic criteria or were subthreshold for the diagnosis. Of the 88 participants who met the full diagnostic criteria for GID in childhood, 12 (13.6%) were gender dysphoric at follow-up and the remaining 76 (86.4%) were no longer gender dysphoric. Of the 51 participants who were subthreshold for the GID diagnosis in childhood, 5 (9.8%) were gender dysphoric at follow-up and the remaining 46 (90.2%) were not. A chi-square analysis revealed that these rates of persistence across subthreshold and threshold groups did not differ significantly, $\chi^2(1) < 1$.

3.3.1.4 Summary of Gender Dysphoric Participants

Table 8 summarizes information on some domains of gender role outcome for the 17 participants classified as having persistent gender dysphoria. There was notable variation within the group of persisters in the extent to which they had socially and medically transitioned to the female gender role.

At follow-up, the majority of the gender dysphoric participants ($n = 9$) were not receiving any medical/biologic treatments to either suppress physical development of secondary sex characteristics/masculinization of their body or to feminize their body. The remaining 8 (47.1%) participants were taking puberty suppressing hormones or were on

cross-sex hormonal therapy to feminize their physical appearance. Of the 9 participants who were not taking puberty suppressing or cross-sex hormones, 6 did not report any attempt to

Table 8

Summary of Gender Dysphoric Participants

ID	Year of childhood assessment	Age at follow-up (in years)	Legal name change	Using female name	Living in female role	On puberty blockers and/or cross-sex hormones	Any surgery
1	1975	18.24	No	No	Androgynous	No	No
2	1979	19.38	No	Yes	Androgynous	No	No
3	1980	35.14	Yes	Yes	Yes	Yes	No
4	1980	19.08	No	Yes	Yes	No	No
5	1983	26.04	No	Yes	Yes	Yes	No
6	1984	18.82	No	No	No data	No	No
7	1984	15.47	No	No	No	No	No
8	1987	23.55	Yes	Yes	Yes	Yes	No
9	1995	22.32	No ^a	Yes	Yes	Yes	No
10	1997	13.62	No	No	No	No	No
11	1997	19.77	No	Yes	Yes	Yes	No
12	1997	16.90	No	No	No	No	No
13	1998	22.18	No	Yes	Partially	No ^b	No
14	2000	17.68	No	Yes	Yes	Yes	No
15	2001	16.61	No	No	No	No	No
16	2002	15.97	No	Yes	Yes	Yes	No
17	2003	15.69	No	Yes	Yes	Yes	No

^aThis participant was in the process of applying for a legal name change.

^bPuberty suppressing hormones (blockers) were recommended.

present socially in the female gender role (e.g., using a female name, living in the female role). Of the remaining 3 participants, 2 were attempting to live socially in the female gender role and data were incomplete for 1 participant. None of the 17 gender dysphoric participants

had received any type of surgery to feminize their appearance (e.g., breast implants, facial feminization surgery, genital reconstruction).

Among the 17 persisters, 11 were using a female name. Of these 11 participants, 2 had legally changed their name on official documents (e.g., driver's license) and 1 was in the process of pursuing a legal name change. Nine of the gender dysphoric participants were living in the female gender role and 4 of them were living in the male gender role. Of the remaining 4 participants, 1 was living partially in the female role (e.g., would sometimes wear make-up and at others times presented androgynously, but did not wear stereotypic female clothing), 2 presented androgynously, and data were not available for 1 participant.

None of the 122 participants classified as desisters desired cross-sex hormones or sex reassignment surgery to feminize their bodies nor did they express a desire to get rid of their male sex characteristics. None of the desisters presented socially as women nor did they express the desire to socially transition to the female gender role (e.g., name change, clothing choice).

3.3.1.5 Odds of Persistent Gender Dysphoria

Formal epidemiological studies on the prevalence of GID in adolescents and adults have not been conducted. Since the 1960s, a number of studies have reported estimated prevalence rates (for a review, see Zucker & Lawrence, 2009). Rates have varied, in part, depending on the inclusion criteria (e.g., including individuals who have had, at least, hormonal treatment vs. only including individuals who have had sex reassignment surgery). For example, De Cuypere et al. (2007) estimated that 1 in 12,900 biological adult males have GID. Weitze and Osburg (1996) estimated a prevalence rate of 1 in 42,000. The estimated prevalence rate in most other studies have fallen within this range (i.e., 1/12900-1/42,000).

Using the prevalence values estimated by De Cuypere et al. and Weitze and Osburg, the odds of persistent gender dysphoria (12.2%) in the present sample was 1794-5840 times higher than it is in biological males in the general population.

3.3.2 Sexual Orientation at Follow-up

On the basis of Kinsey ratings, participants who completed the face-to-face interview were classified into the following three sexual orientation groups for both fantasy and behavior: (1) heterosexual (Kinsey global ratings of 0-1); (2) bisexual/homosexual (Kinsey global ratings of 2-6), and (3) no sexual fantasy or behavior. Throughout this thesis, sexual orientation was classified in relation to birth sex, rather than the participants' subjective sexual identity at follow-up. This is a particularly relevant issue for those participants who had persistent gender dysphoria. For example, if a biological male participant identified as female at follow-up, was sexually attracted to other biological males and self-labeled their sexual identity as heterosexual, they would be classified in the study as homosexual in relation to their birth sex.

Table 9 shows the frequency of ratings for sexual orientation in fantasy. Appendix K lists the individual global fantasy ratings for all participants for whom these data were available. Data were not available for 10 participants,²¹ all of whom were desisters with regard to gender dysphoria. Based on the global ratings for sexual orientation in fantasy, 43 (33.3%) participants were classified as heterosexual in fantasy and 82 (63.6%) were classified as bisexual/homosexual in fantasy. In the remaining 4 (3.1%) cases, the participants were classified as having no sexual fantasies and, therefore, a Kinsey rating could not be assigned. In all 4 cases, the participants were desisters.

²¹For some participants who did not complete the face-to-face assessment, data on sexual orientation were available. In these cases, participants were assigned a Kinsey fantasy rating of 0 for heterosexual sexual orientation and 6 for homosexual sexual orientation.

Table 9
Kinsey Ratings for Sexual Orientation in Fantasy

Variable	Kinsey Rating ^a											
	0		1		2		3		4		5	
	N	%	N	%	N	%	N	%	N	%	N	%
Crush	36	36.7	0	0	2	2.0	4	4.1	2	2.0	11	11.2
Visual	31	31.6	1	1.0	2	2.0	10	10.2	3	3.1	12	12.2
Dreams	13	13.3	1	1.0	1	1.0	4	4.1	3	3.1	3	3.1
Masturbation	21	21.9	2	2.1	3	3.1	6	6.3	2	2.1	7	7.3
Global Fantasy Rating	40	31.0	3	2.3	3	2.3	8	6.2	2	1.6	14	10.9
											55	42.6
											4	3.1

^aKinsey Ratings:

- 0 = Exclusively heterosexual
- 1 = Predominantly heterosexual, only incidentally homosexual
- 2 = Predominantly heterosexual but more than incidentally homosexual
- 3 = Equally homosexual and bisexual
- 4 = Predominantly homosexual, but more than incidentally heterosexual
- 5 = Predominantly homosexual, but incidentally heterosexual
- 6 = Exclusively homosexual

Of the 17 participants classified as gender dysphoric, 1 (5.9%) was heterosexual in fantasy and 16 (94.1%) were bisexual/homosexual in fantasy. Chi-square analysis revealed that the rates of sexual orientation in fantasy across this study, Green (1987), and Wallien and Cohen-Kettenis (2008) did not differ significantly, $\chi^2(2) = 2.82, p > .05$.

Table 10 shows the frequency of ratings for sexual orientation in behavior. Appendix K lists the individual global behavior ratings for all participants for whom these data were available. Data were available for 108 participants. Based on global ratings for sexual orientation in behavior, 29 (26.9%) participants were classified as heterosexual and 51 (47.2%) were classified as bisexual/homosexual. The remaining 28 (25.9%) participants did not report any sexual behaviors in the 12 months preceding the follow-up assessment. For those participants who could be assigned a Kinsey rating (i.e., excluding those participants who did not report any sexual fantasies or behavior or for whom data were not available), the correlation between Kinsey global fantasy and global behavior ratings was very strong, $r(78) = .92, p < .001$.

3.3.2.1 Group Classification as a Function of Gender Identity and Sexual Orientation in Fantasy at Follow-up²²

Combining gender identity (i.e., persister or desister) and sexual orientation in fantasy (i.e., heterosexual or bisexual/homosexual) at follow-up, the participants were classified into one of the following four outcome groups: (1) persistence of gender dysphoria with bisexual/homosexual sexual orientation ($n = 16$); (2) desistence of gender dysphoria with

²² Given the strong correlation between Kinsey fantasy and behavior ratings and that there were less missing data on the Kinsey fantasy variable, participants were classified into one of four outcome groups based on their fantasy ratings. Measuring sexual orientation on the basis of fantasy is methodologically more robust than measuring sexual orientation on the basis of sexual behavior. A person's sexual behavior may be influenced by many factors other than sexual fantasy or sexual feelings, such as moral sense and availability of a sexual partner (LeVay, 2011) and, in general, may be more variable than erotic feelings (Harry, 1985a).

Table 10
Kinsey Ratings for Sexual Orientation in Behavior

Variable	Kinsey Rating ^a														No Sexual Behavior		
	0		1		2		3		4		5		6				
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Dating	27	27.3	0	0	0	0	4	4.0	1	1.0	0	0	0	33	33.3	34	34.0
Holding hands	26	26.3	0	0	0	0	5	5.1	1	1.0	1	1.0	1	35	35.4	31	31.3
Kissing	21	21.2	0	0	0	0	6	6.1	2	2.0	2	2.0	2	34	24.3	34	34.3
Genital/breast contact	13	13.1	0	0	0	0	3	3.0	2	2.0	1	1.0	1	35	35.4	45	45.5
Intercourse	8	8.2	0	0	0	0	3	3.1	2	2.0	0	0	0	27	27.6	58	59.2
Global Behavior Rating	28	25.9	1	0.9	0	0	4	3.7	3	2.8	1	0.9	1	43	39.8	28	25.9

^aKinsey Ratings:

- 0 = Exclusively heterosexual
- 1 = Predominantly heterosexual, only incidentally homosexual
- 2 = Predominantly heterosexual but more than incidentally homosexual
- 3 = Equally homosexual and bisexual
- 4 = Predominantly homosexual, but more than incidentally heterosexual
- 5 = Predominantly homosexual, but incidentally heterosexual
- 6 = Exclusively homosexual

bisexual/homosexual sexual orientation ($n = 66$); (3) desistence of gender dysphoria with heterosexual sexual orientation ($n = 42$); and (4) persistence of gender dysphoria with heterosexual sexual orientation ($n = 1$). The participants who reported no sexual fantasies ($n = 4$) could not be included in this outcome classification. Given that only 1 participant was classified as gender dysphoric with a co-occurring heterosexual sexual orientation (Group 4), this category was excluded from subsequent analyses that compared these outcome groups.

3.4 Demographic Characteristics

3.4.1 Demographic Characteristics in Childhood as a Function of Gender Identity and Sexual Orientation in Fantasy

Table 11 shows the demographic variables in childhood as a function of group. One-way ANOVAs and chi-square were conducted to evaluate whether the outcome groups differed on demographic variables in childhood. The groups differed significantly on four of the five childhood demographic variables ($ps < .05$). The group comparison on ethnic background was not significant.

Duncan's multiple range test for unequal Ns showed that the bisexual/homosexual persisters were, on average, significantly older at the time of the childhood assessment than both the heterosexual desisters and the bisexual/homosexual desisters, who did not differ significantly from each other. Regarding IQ, the bisexual/homosexual desisters had, on average, a higher IQ than the bisexual/homosexual persisters but did not differ significantly from the heterosexual desisters. There was no significant difference in childhood IQ score between bisexual/homosexual persisters and heterosexual desisters. The bisexual/homosexual persisters were significantly more likely to come from a lower social class background compared to the heterosexual desisters and the bisexual/homosexual

Table 11

Demographic Characteristics in Childhood and at Follow-up as a Function of Group

		Group			<i>F</i> or χ^2	<i>p</i>	η^2 or Cramer's V
Variable		Persisters Bisexual/ Homosexual (<i>n</i> = 16)	Desisters Bisexual/ Homosexual (<i>n</i> = 66)	Desisters Heterosexual (<i>n</i> = 42)			
<u>Childhood</u>							
Age (in years)	<i>M</i>	8.85	6.96	7.49	3.57	.031	.06
	<i>SD</i>	1.67	2.69	2.62			
IQ ^a	<i>M</i>	101.63	110.20	103.18	3.77	.026	.06
	<i>SD</i>	14.81	14.56	15.16			
Social Class ^b	<i>M</i>	23.76	44.97	39.44	15.30	<.001	.20
	<i>SD</i>	10.22	13.64	15.91			
Year of Assessment	<i>M</i>	1990.85	1989.83	1987.80	1.33	ns	-
	<i>SD</i>	9.65	6.07	8.68			
Marital Status ^c							
Two-parent	N (%)	7 (43.8)	49 (74.2)	24 (57.1)	6.74	.034	.23
Other	N (%)	9 (56.3)	17 (25.8)	18 (42.9)			
Ethnicity							
Caucasian	N (%)	14 (87.5)	58 (87.9)	32 (76.2)	2.77	ns	-
Other	N (%)	2 (12.5)	8 (12.1)	10 (23.8)			
<u>Follow-up</u>							
Age at follow-up (in years) ^d	<i>M</i>	20.32	22.13	17.85	10.41	<.001	.15
	<i>SD</i>	5.67	4.97	3.95			

Table 11

Demographic Characteristics in Childhood and at Follow-up as a Function of Group

Variable		Group			<i>F</i> or χ^2	<i>p</i>	η^2 or Cramer's V
		Persisters Bisexual/ Homosexual (<i>n</i> = 16)	Desisters Bisexual/ Homosexual (<i>n</i> = 66)	Desisters Heterosexual (<i>n</i> = 42)			
IQ at follow-up ^{a,e,f}	<i>M</i>	99.07	110.47	104.19	3.82	.025	.07
	<i>SD</i>	16.29	13.54	17.50			
Follow-up interval (in years)	<i>M</i>	11.47	15.17	10.36	9.63	<.001	.04
	<i>SD</i>	6.77	6.03	4.85			
Social Desirability ^g	<i>M</i>	.44	.43	.52	2.50	ns	-
	<i>SD</i>	.17	.18	.19			

^aFull-Scale IQ was obtained with age-appropriate Wechsler intelligence scales.^bHollingshead's (1975) Four Factor Index of Social Status; absolute range, 8-66.^cOther included the following family constellations: single parent, separated, divorced, living with relatives, or in the care of a child protection agency.^dInterval denotes the time between childhood assessment and follow-up assessment.^eFull Scale IQ estimated using four subtests: Vocabulary, Comprehension, Block Design and Object Assembly.^fIQ were only available for participants who completed the face-to-face assessment.^gMeasured using Marlowe-Crowne Social Desirability Scale (Crowne & Marlow, 1960) and expressed as a proportion score. Absolute range, .00 - 1.00. Higher score indicates a greater propensity to give socially desirable responses.

desisters, who did not differ significantly from each other. The bisexual/homosexual desisters were more likely to be living with both parents compared to the bisexual/homosexual persisters. There was no significant difference on marital status between the two desister groups.

As shown in Table 12, the demographic variables on which the three groups differed—age at assessment, IQ, social class, and marital status—were significantly correlated. To evaluate the influence of these variables on group outcome at follow-up, a multinomial logistic regression was performed. It can be seen from Table 13 that only social class had a significant contribution to the prediction of group outcome at follow-up. The bisexual/homosexual persisters had a 13% increase in odds of coming from a lower social class background compared to the bisexual/homosexual desisters. However, social class did not predict outcome when the two desister groups were compared. Figure 1 shows the distribution of social class across the outcome groups.

Table 12

Correlation Matrix of Childhood Demographic Variables on which the Groups Differed

Measures	1	2	3	4
1. Age at assessment	-	-.42***	-.44***	.32***
2. IQ		-	.54***	-.35***
3. Social Class			-	-.58***
4. Marital Status				-

p < .001

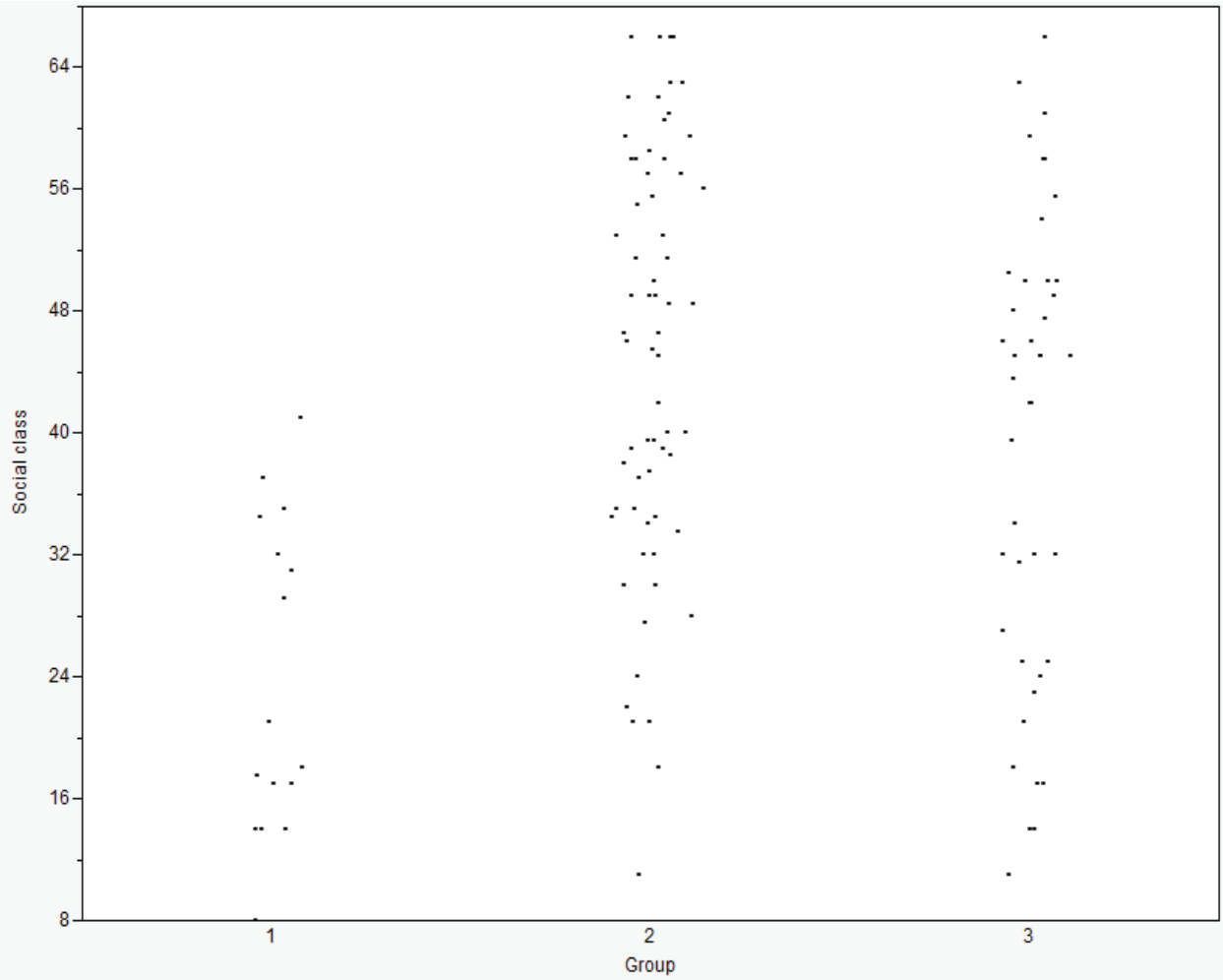


Figure 1. Distribution of social class for the outcome groups at follow-up.

- 1 = Bisexual/homosexual persisters ($n = 16$; $M = 23.76$, $SD = 10.22$)
- 2 = Bisexual/homosexual desisters ($n = 66$; $M = 44.97$, $SD = 13.64$)
- 3 = Heterosexual desisters ($n = 42$; $M = 39.44$, $SD = 15.91$)

Table 13

Multinomial Logistic Regression Predicting Group Outcome at Follow-up

Predictor	Bisexual/Homosexual Persisters					Heterosexual Desisters				
	<i>B</i>	SE	Wald	<i>p</i>	<i>e^B</i>	<i>B</i>	SE	Wald	<i>p</i>	<i>e^B</i>
Age at Assessment	0.11	0.14	0.62	ns	1.12	-0.02	0.09	0.03	ns	.98
IQ	0.02	0.03	0.85	ns	1.02	-0.02	0.02	1.91	ns	.98
Social Class	-0.14	0.04	13.66	<.001	.87	-0.01	0.02	0.13	ns	.99
Marital Status	-0.76	0.80	0.88	ns	.47	0.43	0.52	0.70	ns	1.54

Note. Reference group is the Bisexual/homosexual Desisters. This group was chosen as the reference because it represents the largest group size. Desistence of GID with a bisexual/homosexual sexual orientation is also the most common long-term outcome for children with GID.

3.4.2 Demographic Characteristics at Follow-up as a Function of Gender Identity and Sexual Orientation in Fantasy

Table 11 also shows the demographic variables of age and IQ at follow-up as a function of group. One-way ANOVAs revealed that both variables differed significantly among the three groups ($ps < .01$). Duncan's multiple range test for unequal Ns showed that the heterosexual desisters were, on average, younger than both the bisexual/homosexual persisters and the bisexual/homosexual desisters, who did not differ significantly from each other.

Regarding IQ at follow-up, the results were similar to those for IQ in childhood. The bisexual/homosexual desisters had, on average, higher IQ than the bisexual/homosexual persisters but did not differ significantly from the heterosexual desisters. There was no significant difference in IQ between the bisexual/homosexual persisters and the heterosexual desisters.

3.5 Social Desirability

Table 11 shows the mean proportion score on the measure of social desirability as a function of group. A one-way ANCOVA for Group (with age at assessment, age at follow-up, IQ in childhood, IQ at follow-up, social class, and marital status⁶ covaried) was conducted to evaluate the proportion of socially desirable responses on the Marlow-Crowne Social Desirability Scale for participants according to their group classification at follow-up. There was no significant difference in the proportion of socially desirable responses on the Marlow-Crowne Social Desirability Scale as a function of gender identity and sexual orientation in fantasy ($p = .089$).

3.6 Childhood Sex-Typed Behavior

3.6.1 Childhood Sex-Typed Behavior as a Function of Gender Identity and Sexual

Orientation at Follow-up

Table 14 shows the means and *SDs* (for continuous variables) or percentage scores (for dichotomous variables) of the childhood sex-typed variables obtained at the assessment as a function of the three outcome groups. ANCOVAs (with age at assessment, IQ, social class, and marital status²³ covaried) or chi-square were used to examine whether the groups differed on any of the reported variables. The corresponding *F* or chi-square values are also shown.

Of the 9 sex-typed measures, there was a significant difference between the groups on four child-report measures (first drawn person on the Draw-a-Person, free play, Gender Identity Interview, and cross-sex peer preference on the Playmate and Play Style Preferences Structured Interview, and one parent-report measure (Gender Identity Questionnaire

²³ The ANCOVA model was adjusted to accommodate a categorical covariate.

Table 14
Childhood Sex-Typed Behavior as a Function of Group

Variable		Persists Bisexual/ Homosexual	Desists Bisexual/ Homosexual	Desists Heterosexual	<i>F</i> or χ^2	<i>p</i>	η^2 or Cramer's <i>V</i>
DSM Diagnosis ^a							
Threshold for GID	N (%)	12 (75.0)	46 (69.7)	23 (54.8)	3.29	ns	-
Subthreshold for GID		4 (25.0)	20 (30.3)	19 (45.2)			
Child-report measures							
Draw-a-Person							
Same-Sex Person Drawn First	N (%)	4 (25.0)	27 (40.9)	25 (59.5)	6.61	.037	.23
Cross-Sex Person Drawn First		12 (75.0)	39 (59.1)	17 (40.5)			
Free Play Task ^b							
	M	.24	.23	-.06	7.82	.001	.13
	SD	.43	.62	.69			
	N	13	60	37			
Rorschach Difference Score ^c							
	M	.40	.97	-.08	.53	ns	-
	SD	4.75	4.07	3.11			
	N	15	61	36			
Gender Identity Interview ^d							
	M	9.78	5.91	7.43	4.24	.018	.11
	SD	5.63	5.31	7.10			
	N	9	46	21			

Table 14

Childhood Sex-Typed Behavior as a Function of Group

Variable		Persisters Bisexual/ Homosexual	Desisters Bisexual/ Homosexual	Desisters Heterosexual	<i>F</i> or χ^2	<i>p</i>	η^2 or Cramer's <i>V</i>
Playmate and Playstyle Preferences	M	9.75	8.13	8.08	3.54	.042	.20
Structured Interview: Cross-sex Peer Play ^e	SD	4.83	5.78	5.57			
	N	8	16	12			
Playmate and Playstyle Preferences	M	8.75	7.00	6.67	2.55	.096	.15
Structured Interview: Cross-sex toy play ^f	SD	2.43	2.92	3.37			
	N	8	16	12			
Parent-report measures							
Gender Identity Questionnaire for Children ^g	M	2.40	2.88	2.87			
	SD	.49	.58	.85	4.05	.021	
	N	10	53	22			
Temperament: Activity Level ^h	M	2.95	3.08	3.03	.593	ns	-
	SD	.41	.49	.59			
	N	15	65	41			

^aFor diagnosis, GID means that the patient met complete DSM-III, DSM-III-R, or DSM-IV criteria for GID.^bDifference between cross-sex and same-sex play during a free-play task. Positive score indicates more cross-sex play.^cDifference between number of same-sex and cross-sex responses. Positive score indicates more cross-sex responses.^dAbsolute range, 0-24. A higher score reflects more gender identity confusion.^eAbsolute range, 0-14. A higher score indicates more cross-sex playmate/peer choices.^fAbsolute range, 0-14. A higher score indicates more cross-sex toy choices.^gAbsolute range, 1-5. A lower score indicates more cross-gender behavior.^hAbsolute range, 1-5. A higher score indicates higher activity level.

for Children). The ANCOVA for the cross-sex toy preference on the Playmate and Play Style Preferences Structured Interview approached significance ($p = .096$). The significant one-way ANCOVAs were followed up with post hoc analyses using lmatrix commands and the significant chi-square was followed-up with pair-wise chi-square comparisons.

On the Draw-a-Person, there was one significant post-hoc contrast. The bisexual/homosexual persisters were, on average, significantly more likely to draw a female first compared to the heterosexual desisters ($p = .04$). The comparison between the bisexual/homosexual desisters and heterosexual desisters approached significance ($p = .09$), with the bisexual/homosexual desisters showing a greater tendency to draw a female first. The comparison between the bisexual/homosexual persisters and bisexual/homosexual desisters was not significant ($p > .05$). On the free play measure, all post-hoc contrasts were significant. The bisexual/homosexual persisters displayed, on average, more cross-sex play than did the bisexual/homosexual desisters and the heterosexual desisters. The latter two groups differed significantly from each other; the bisexual/homosexual desisters displayed, on average, significantly more cross-sex play than did the heterosexual desisters. On the Gender Identity Interview, a semi-structured interview that assesses gender identity, feelings of gender confusion, and gender dysphoria, the bisexual/homosexual persisters reported, on average, significantly more gender confusion than did the bisexual/homosexual desisters. The post-hoc comparison between the bisexual/homosexual persisters and the heterosexual desisters approached significance ($p = .054$), with the bisexual/homosexual persisters reporting more gender confusion than the heterosexual desisters. The comparison between the bisexual/homosexual desisters and heterosexual desisters was not significant. There was also significant group difference on the peer preference domain of the Playmate and Play

Style Preferences Structured Interview. The bisexual/homosexual persisters had, on average, significantly more cross-sex peer preference compared to the bisexual/homosexual desisters and the heterosexual desisters, who did not differ significantly from each other. On the Gender Identity Questionnaire for Children, a parent-report measure of cross-gender interest and identification, the bisexual/homosexual persisters were reported as significantly more cross-gendered than the bisexual/homosexual desisters and the heterosexual desisters. The latter two groups did not differ significantly from each other.

As can be seen from Table 15, the childhood sex-typed behavior measures on which the groups differed were significantly correlated.²⁴ From these six measures (first drawn

Table 15
Correlation Matrix of Childhood Sex-Typed Measures on which the Groups Differed

Measures	1	2	3	4	5	6
1. Draw-a-Person	-	.46***	.36**	.58***	.42*	-.30**
2. Free Play Task		-	.43***	.68***	.55**	-.42***
3. Gender Identity Interview			-	.56***	.47**	-.35**
4. Playmate and Playstyle Preferences Structured Interview: Cross-sex peer play				-	.76***	-.47**
5. Playmate and Playstyle Preferences Structured Interview: Cross-sex toy play					-	-.46**
6. Gender Identity Questionnaire for Children						-

Note. The *n* values vary for each variable.

* $p < .05$, ** $p < .01$, *** $p < .001$

person on the Draw-a-Person, free play, Gender Identity Interview, cross-sex peer preference on the Playmate and Play Style Preferences Structured Interview,²¹ cross-sex toy preference

²⁴ Although the groups did not differ significantly on cross-sex toy preference on the PPPSI, this measure is included here because there was a trend in the direction of a significant group difference.

on the Playmate and Play Style Preferences Structured Interview, and the Gender Identity Questionnaire for Children), a composite score of childhood sex-typed behavior was derived for each participant by taking the average of the six variables²⁵ (each expressed as z-scores). Thus, the composite score was expressed as a z-score. A higher composite z-score indicates more cross-gender behavior at assessment (Fig. 2).

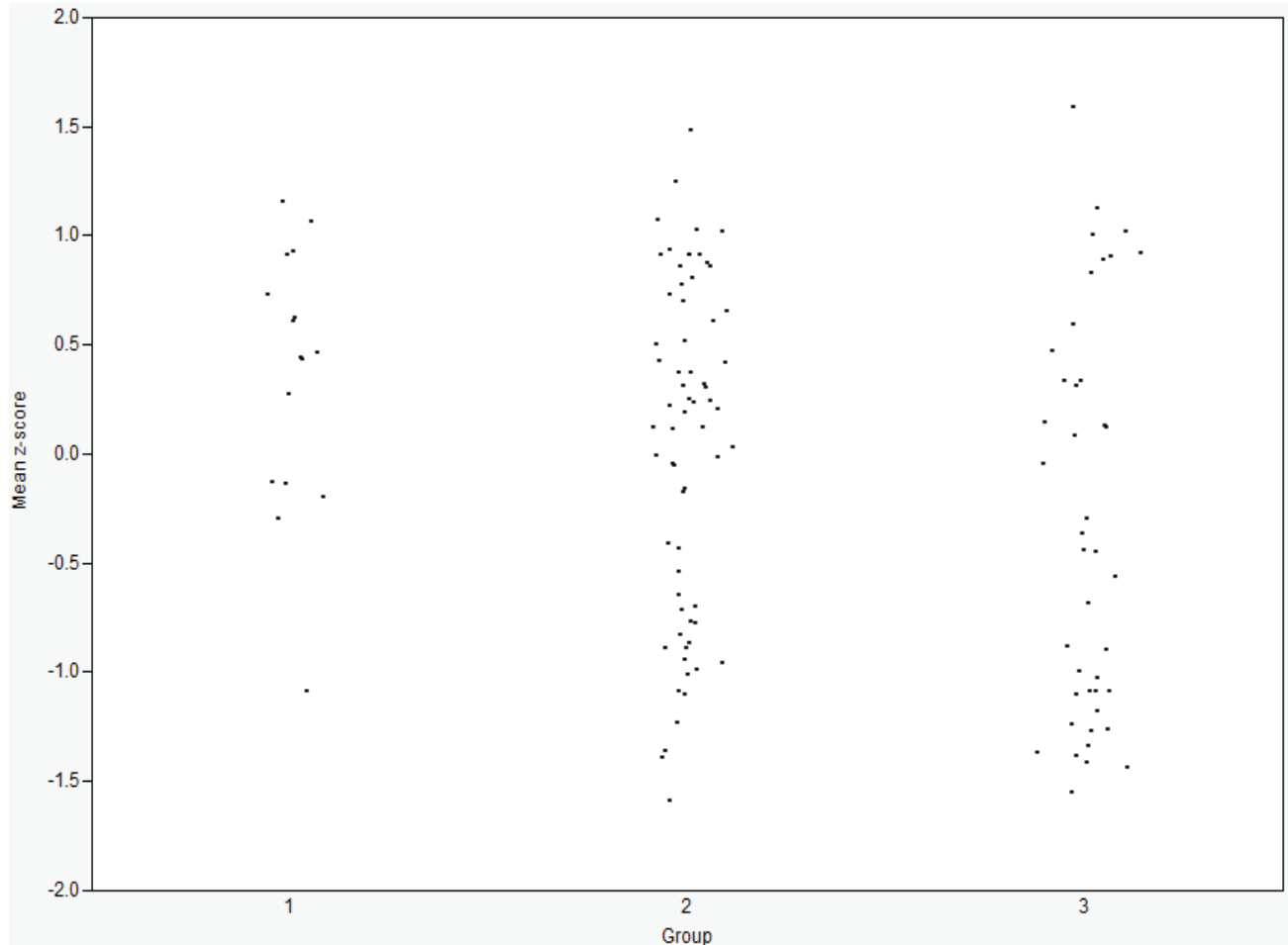


Figure 2. Distribution of the mean composite z-score for the outcome groups at follow-up.

- 1 = Bisexual/homosexual persisters ($n = 16$; $M = .36$, $SD = .60$)
 2 = Bisexual/homosexual desisters ($n = 66$; $M = .03$, $SD = .77$)
 3 = Heterosexual desisters ($n = 42$; $M = -.32$, $SD = .90$)

²⁵ For some participants, data were not available on all six measures. In these cases, the composite score was the average of the number of variables for which there were data.

To evaluate the influence of childhood sex-typed behavior and demographic variables on group outcome at follow-up, a multinomial logistic regression was performed using the composite score and the demographic variables on which the groups differed²⁶—age at assessment, IQ, and social class—as predictor variables. It can be seen from Table 16 that both social class and the composite score of childhood sex-typed behavior were significant predictors of group outcome at follow-up in the first model which compared the bisexual/homosexual persisters to the bisexual/homosexual desisters.

Table 16

Multinomial Logistic Regression Predicting Group Outcome at Follow-up

Predictor	Bisexual/Homosexual Persisters					Heterosexual Desisters				
	<i>B</i>	SE	Wald	<i>p</i>	e^B	<i>B</i>	SE	Wald	<i>p</i>	e^B
Age at Assessment	.26	.16	2.90	.09	1.30	-.14	.11	1.55	.21	.87
IQ	.02	.03	.58	.45	1.02	-.03	.01	2.77	.10	.97
Social Class	-.12	.03	12.28	<.001	.89	-.01	.01	.51	.47	.99
Composite Z-score	1.32	.55	5.82	.02	3.74	-.66	.31	4.38	.04	.52

Note. Reference group is the Bisexual/homosexual Desisters. This group was chosen as the reference because it represents the largest group size. Desistence of GID with a bisexual/homosexual sexual orientation is also the most common long-term outcome for children with GID.

The bisexual/homosexual persisters had a 274% increase in odds of having a higher composite score (i.e., more childhood cross-gender behavior) and 11% increase in odds of coming from a lower social class compared to the bisexual/homosexual desisters. Age at childhood assessment and IQ did not have a significant effect on group outcome (both *ps* > .05). In the second model, which compared the heterosexual desisters to the bisexual/

²⁶ A preliminary analysis with marital status included as a predictor variable showed that this variable did not have a significant effect and was, therefore, excluded in the final regression model.

homosexual desisters, the only significant predictor of group outcome was the composite measures of sex-typed behavior. The bisexual/homosexual desisters had a 48% increase in odds of having a higher composite score compared to the heterosexual desisters.

3.6.2 Childhood Sex-Typed Behavior and Year of Assessment

The childhood assessment data were collected over the course of three decades, 1975-2004. Using correlation analysis, I assessed whether a relationship existed between year of assessment and scores on measures of sex-typed behavior. Across the entire sample, there was no significant correlation between year of assessment and any of the nine measures of childhood sex-typed behavior, all $ps > .05$. However, three correlations approached significance: free play ($p = .05$), the Gender Identity Questionnaire for Children ($p = .08$), and the cross-sex peer preference on Playmate and Play Style Preferences Structured Interview ($p = .08$). Across all three measures, there was a trend for participants with a later year of assessment (i.e., assessed more recently) to have had, on average, more childhood cross-gender behaviors compared to participants assessed earlier in the data collection period.

3.7 Peer Relations in Childhood

In the present study, we examined the quality of participants' childhood peer relations by computing the Peer Relations Scale (Zucker, Bradley, & Sanikhani, 1997). In an effort to identify the relationship between peer relations and age across the entire sample of boys, participants' age at childhood assessment and score on the Peer Relations Scale was correlated. The correlation was significant, $r(121) = .58, p < .001$, with older boys having poorer peer relations than younger boys. To examine the relationship between peer relations and behavior problems in childhood, participants Peer Relations Score was correlated with the sum of items rated as 1 or 2 on the CBCL, with the three items contributing to the Peer

Relations Scale removed to prevent artificial inflation of the sum score.²⁷ The correlation was significant, $r(121) = .43, p < .001$.

A one-way ANCOVA (with age at assessment, IQ in childhood, social class, and marital status co-varied) was conducted to examine whether the three outcome groups at follow-up differed in the quality of their peer relations in childhood. The ANCOVA was not significant, $F(2, 120) < 1$.

3.8 Childhood Behavior Problems as a Function of Gender Identity and Sexual Orientation at Follow-up

Table 17 shows the maternal ratings on the Child Behavior Checklist (CBCL) as a function of group. ANCOVAs (with age at assessment, IQ, social class, and marital status²⁸ co-varied) were used to examine whether the groups differed on any of the reported childhood variables. The corresponding F values are also reported.

One-way ANCOVAs for Group revealed that there were no significant differences between the three groups on Internalizing T score, Externalizing T score or Total Problems T score at the childhood assessment ($ps > .05$). Table 17 also shows the percentage of participants in each group who fell within the clinical range (T score $> 90^{\text{th}}$ percentile) according to their Internalizing, Externalizing, and Total Problems T scores. For the bisexual/homosexual persisters, 62.5%-68.8% fell within the clinical range depending on whether they were classified according to their Internalizing T score, Externalizing T Score or Total T score. For the bisexual/homosexual desisters, 40.9%-42.4% were within the

²⁷ I did not perform correlation analyses between peer relations and Internalizing and Externalizing T score because the three items from the Peer Relations Scale loaded on at least one of the broad-band factors and it would have been too cumbersome to re-score all the CBCLs with these items removed.

²⁸ The ANCOVA model was adjusted to accommodate a categorical covariate.

Table 17
Behavior Problems in Childhood and Follow-up as a Function of Group

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Variable	Group													
	Persisters				Desisters				Desisters					
	Bisexual/Homosexual				Bisexual/Homosexual				Heterosexual					
	<i>M</i>	<i>SD</i>	Clinical Range (%) ^a	<i>N</i>	<i>M</i>	<i>SD</i>	Clinical Range (%) ^a	<i>N</i>	<i>M</i>	<i>SD</i>	Clinical Range (%) ^a	<i>N</i>	<i>F</i>	<i>p</i>
Childhood														
Internalizing <i>T</i>	64.69	9.26	68.8 ^b	16	60.39	8.90	42.4 ^b	66	64.45	10.03	54.8 ^b	42	1.14	ns
Externalizing <i>T</i>	65.88	9.43	62.5 ^c	16	59.39	10.98	42.4 ^c	66	61.67	11.21	42.9 ^c	42	<1	ns
Total <i>T</i>	66.75	10.76	62.5 ^d	16	61.05	10.83	40.9 ^d	66	64.48	11.57	50.0 ^d	42	<1	ns
Follow-up Parent Report														
Internalizing <i>T</i>	59.23	8.60	23.1 ^e	13	57.91	11.93	36.4 ^e	44	55.44	12.19	24.2 ^e	32	1.47	ns
Externalizing <i>T</i>	61.92	8.18	23.1 ^f	13	55.73	11.40	22.7 ^f	44	53.94	10.39	15.2 ^f	32	1.10	ns
Total <i>T</i>	62.54	8.21	38.5 ^g	13	55.95	12.11	20.5 ^g	44	55.31	13.10	27.3 ^g	32	<1	ns
Follow-up Self Report														
Internalizing <i>T</i>	62.87	13.83	46.7 ^h	15	55.77	9.95	20.0 ^h	48	48.44	10.87	11.1 ^h	36	5.05	.008
Externalizing <i>T</i>	59.00	13.34	53.3 ⁱ	15	55.73	11.09	24.0 ⁱ	48	51.28	9.38	5.6 ⁱ	36	<1	ns
Total <i>T</i>	61.53	13.88	46.7 ^j	15	54.90	10.64	18.0 ^j	48	49.39	10.52	11.1 ^j	36	2.60	.08

^a*T* score > 90th percentile.

^b $\chi^2(2) = 4.15, ns.$

^c $\chi^2(2) = 2.23, ns.$

^d $\chi^2(2) = 2.68, ns.$

^e $\chi^2(2) = 1.66, ns.$

^f $\chi^2(2) < 1, ns.$

^g $\chi^2(2) = 1.79, ns.$

^h $\chi^2(2) = 8.17, p = .017.$

ⁱ $\chi^2(2) = 14.47, p = .001.$

^j $\chi^2(2) = 8.63, p = .013.$

clinical range and, for the heterosexual desisters, 42.9%-54.8% were within the clinical range. These percentages did not differ significantly (see chi-square results in Table 17, footnotes b, c, and d).

3.9 Psychosexual Measures as a Function of Group

Table 18 summarizes six psychosexual variables obtained at follow-up as a function of group: (1) Gender Dysphoria, (2) the Recalled Childhood Gender Identity/Gender Role Questionnaire, (3) Erotic Response and Orientation Scale, Homoerotic Score, (4) Erotic Response and Orientation Scale, Heteroerotic Score, (5) Sexual History Questionnaire, Homoerotic Scale, and (6) Sexual History Questionnaire, Heteroerotic Scale. Table 18 also summarizes the results of a parent-report measure of gender role behavior at follow-up.

A series of ANCOVAs with age at assessment, IQ in childhood, social class, age at follow-up, IQ at follow-up, and marital status co-varied were conducted to evaluate whether the three groups differed significantly on any of the self-report measures. There was a significant main effect for group on all ANCOVAs. The significant ANCOVAs were followed up with post-hoc analyses using Imatrix commands, the results of which are reported below. For the Erotic Response and Orientation Scale (EROS), significant Group x EROS (homoerotic vs. heteroerotic) interaction was decomposed with between-and within-group pair-wise comparisons. Similarly, for the Sexual History Questionnaire (SHQ), significant Group x SHQ (homoerotic vs. heteroerotic) interaction was decomposed with between-and within-group pair-wise comparisons.

3.9.1 Gender Dysphoria

On the gender dysphoria measure,²⁹ there was a significant main effect for Group,

²⁹ This is a proportion score which represents participants' scores on the GIQAA or the GDQ, depending on which measure was administered.

Table 18

Psychosexual Measures as a Function of Group

		Group					
Variable		Persisters Bisexual/ Homosexual	Desisters Bisexual/ Homosexual	Desisters Heterosexual	<i>F</i>	<i>p</i>	η^2
<u>Self-Report</u>							
Gender Dysphoria ^a	M	.66	.03	.01	259.85	<.001	.85
	SD	.22	.05	.02			
	N	15	49	36			
RCGI ^b	M	1.96	3.01	3.75	30.20	<.001	.51
	SD	.44	.51	.68			
	N	11	42	15			
EROS					64.30	<.001	.58
EROS: Homoerotic ^c	M	3.53	3.39	1.04			
	SD	1.25	.96	.14			
	N	15	49	37			
EROS: Heteroerotic ^c	M	1.23	1.83	2.93			
	SD	.42	1.00	1.08			
	N	15	49	37			
SHQ					26.40	.001	.37
SHQ: Homoerotic ^d	M	3.38	2.46	1.00			
	SD	1.25	1.19	.00			
	N	15	49	36			
SHQ: Heteroerotic ^d	M	1.37	1.80	2.02			
	SD	.56	.95	.88			
	N	15	49	36			

Table 18

Psychosexual Measures as a Function of Group

		Group					
Variable		Persisters	Desisters	Desisters	<i>F</i>	<i>p</i>	η^2
		Bisexual/ Homosexual	Bisexual/ Homosexual	Heterosexual			
<u>Parent-Report</u>							
GIDRQ-Ad ^c	M	2.30	3.28	3.85	23.28	<.001	.37
	SD	1.09	.58	.52			
	N	12	44	31			

Note. RCGI = Recalled Childhood Gender Identity/Gender Role Questionnaire; EROS = Erotic Response and Orientation Questionnaire; SHQ = Sexual History Questionnaire; GIGRQ-Ad = Gender Identity/Gender Role Questionnaire for Adolescents.

^aAbsolute range, .00-1.00. A higher score indicates more gender dysphoria. This is a proportion score which represents participants' scores on the Gender Identity/Gender Role Questionnaire for Adolescents and Adults or Gender Dysphoria Questionnaire, depending on which measure was administered.

^bAbsolute range, 1-5. A lower score indicates more recalled childhood cross-gender behavior.

^cAbsolute range, 1.5. A higher score indicates more frequent sexual fantasies.

^dAbsolute range, 1.5. A higher score indicates more frequent sexual behavior.

^eFor this measure, there was no absolute range, because one item did not have a scale—it asked parents to report on the number of male and/or female peers their child has. In this study, the actual range, across all three groups, was .78-4.80, with higher score reflecting more gender-typical behavior.

$F(2, 99) = 259.85, p < .001$. The strength of the relationship between Group and the gender dysphoria score, as assessed by partial η^2 , was strong, with Group accounting for 85.1% of the variance in gender dysphoria scores. Post-hoc analyses using *lmatrix* commands showed that the bisexual/homosexual persisters reported, on average, significantly more concurrent gender dysphoria than did the bisexual/homosexual desisters and the heterosexual desisters (both $ps < .001$).

3. 9.1.1 "Caseness" of Gender Dysphoria on the Gender Identity Questionnaire for Adolescents and Adults

Deogracias et al. (2007) suggested that a mean score of ≤ 3 on the Gender Identity

Questionnaire for Adolescents and Adults³⁰ can be used to determine whether a participant was gender dysphoric. In subsequent studies examining the psychometric properties of the Gender Identity Questionnaire for Adolescents and Adults (Singh et al., 2010; Singh, McMain, & Zucker, 2011), this criterion for “caseness” of gender dysphoria was also applied. In the present study, the Gender Identity Questionnaire for Adolescents and Adults data were available for 64 participants (12 persisters, 52 desisters).

As shown in Fig. 3, for the 12 persisters who completed the Gender Identity Questionnaire for Adolescents and Adults, all but 2 participants³¹ had scores lower than 3.00 ($M = 2.50$, $SD = .78$; range, 1.78-4.30), whereas all of the participants classified as desisters (and for whom data were available) had a mean score greater than 3.00 ($M = 4.86$, $SD = .18$; range, 4.19-5.00). Therefore, using the above-stated criterion for caseness, 83.3% of the bisexual/homosexual persisters (for whom data were available) met the criterion compared to 0% of the bisexual/homosexual desisters and 0% of the heterosexual desisters.

The group differences on mean scores on the Gender Identity Questionnaire for Adolescents and Adults were significant. A one-way ANCOVA (with age at assessment, IQ in childhood, social class, age at follow-up, IQ at follow-up, and marital status co-varied) for Group was significant, $F(2, 61) = 206.103$, $p < .001$, partial $\eta^2 = .89$. Post hoc analyses using lmatrix commands revealed two significant contrasts. The bisexual/homosexual persisters, on average, reported significantly more concurrent gender dysphoria than did the bisexual/homosexual desisters and the heterosexual desisters (both $ps < .001$).

³⁰ Absolute range on the GIQAA is 1-5, with a lower score reflecting more gender dysphoria.

³¹ In one case, although the participant (in Group 1) did not endorse significant gender dysphoria on the Gender Identity Questionnaire for Adolescents and Adults, he was classified as a persister because subsequent follow-up information provided by the participant himself at later dates indicated that he was, in fact, struggling with his gender identity. Regrettably, the Gender Identity Questionnaire for Adolescents and Adults was not re-administered to him. In the second case, the participant was the only heterosexual desister (Group 4).

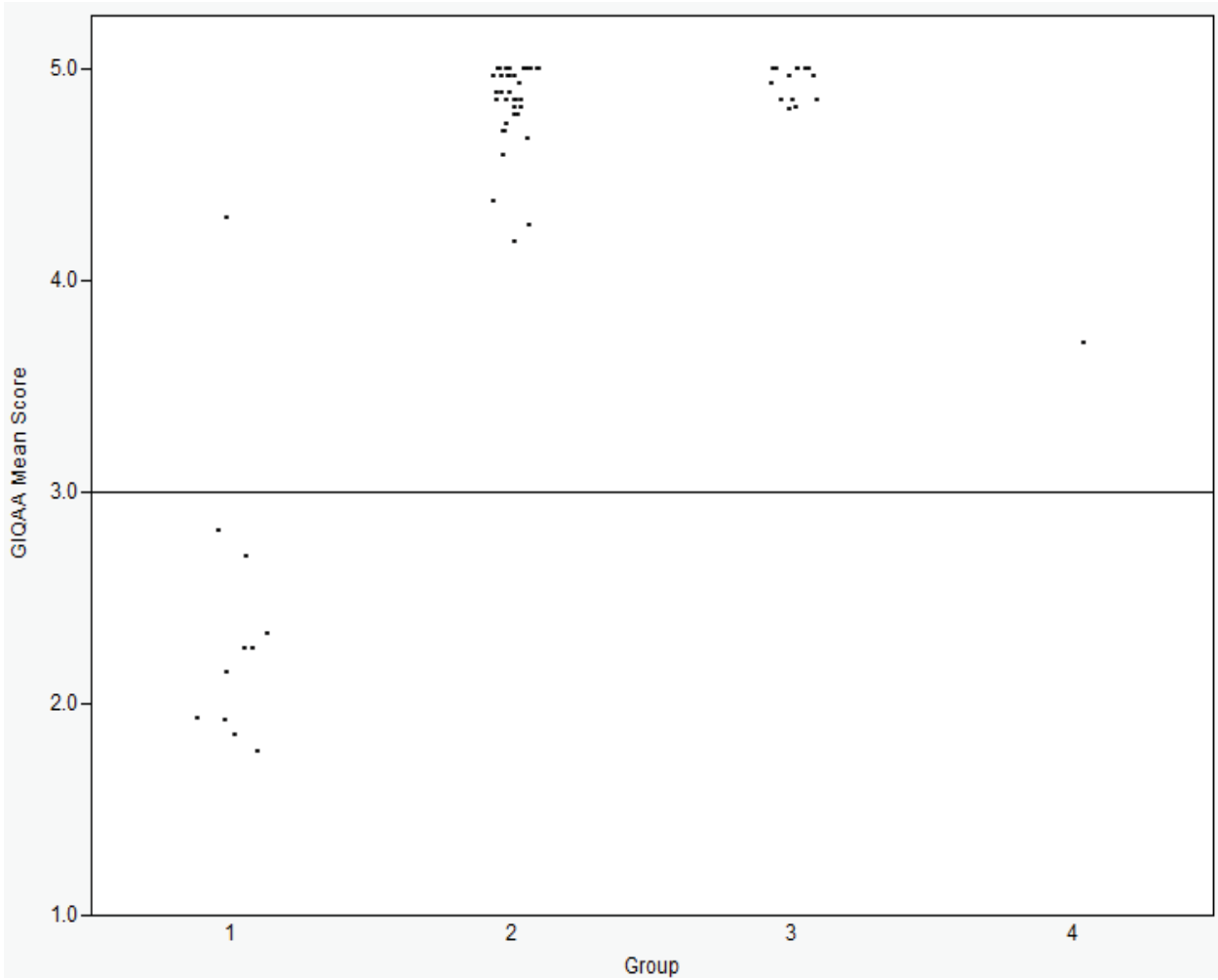


Figure 3. Distribution of the mean scores on the Gender Identity Questionnaire for Adolescents and Adults for the outcome groups at follow-up.

- 1 = Bisexual/homosexual persisters ($n = 16$)
- 2 = Bisexual/homosexual desisters ($n = 66$)
- 3 = Heterosexual desisters ($n = 42$)
- 4 = Heterosexual persisters ($n = 1$)

3.9.2 Recalled Childhood Sex-Typed Behavior

Table 19 shows the mean Recalled Childhood Gender Identity/Gender Role Questionnaire (RCGI) Factor 1 score for the entire sample, which pertained to the participants' recollections of their sex-typed behaviors in childhood. A lower score on the RCGI indicates more recalled cross-gender identity/gender role. This mean score can be

Table 19

Mean Factor 1 Score on the Recalled Childhood Gender Identity/Gender Role Questionnaire

Group	M	SD	d^b
Total follow-up sample ^a ($n = 71$)	3.03	.77	
Childhood Diagnosis			
Threshold for GID ($n = 51$)	2.94	.75	.42 ^c
Subthreshold for GID ($n = 20$)	3.27	.78	
(Clinical Control adolescent males ($n = 40$)) ^d	(4.31)	(.36)	
(Clinical Control adult males ($n = 37$)) ^d	(4.09)	(.68)	
(GID adolescent males ($n = 19$)) ^d	(2.64)	(.93)	
(GID adult males ($n = 33$)) ^d	(2.74)	(.84)	

Note. Absolute range, 1.00-5.00. A lower score indicates more recalled cross-gender identity/gender role.

^aSome participants did not complete the RCGI because its development succeeded the beginning of data collection.

^bCalculated as $M_1 - M_2 / SD_{\text{comparison group}}$.

^cReference group was the participants who were subthreshold for the GID diagnosis in childhood.

^dSingh et al. (2010).

compared with a sample of clinical control males (i.e., males with mental health concerns other than GID) unselected for their gender identity or sexual orientation reported on in Singh et al. (2010) and also shown in Table 19. These clinical control males were collected as part of a research study which examined the psychometric studies of the Gender Identity/Gender Role Questionnaire for Adolescents and Adults and which was conducted in our Gender Identity Service (see Singh et al., 2010). Thus, the RCGI data from these clinical control males were available for comparison to the males in the present follow-up study. It can be seen that, as a group, the males in the present study recalled relatively more childhood cross-gender behavior ($M = 3.03$, $SD = .77$) compared to clinical control adult males ($M = 4.09$, $SD = .68$) and clinical control adolescent males ($M = 4.31$, $SD = .36$). With age covaried³², the mean RCGI score across these three groups was significantly different, $F(2, 148) = 59.71$, $p < .001$, partial $\eta^2 = .45$. Post hoc analyses using lmatrix commands revealed two significant contrasts. The males in the present study recalled, on average, significantly more childhood cross-gender behavior compared to clinical control adult males and adolescent males (both $ps < .001$). The two clinical control groups of males did not differ significantly from each other ($p > .05$). The recollections of childhood sex-typed behavior by the males in this sample was similar to the childhood recollections of other biological males with GID assessed for the first time in adolescence or adulthood (Table 19) and reported on in Singh et al. (2010), $F(2, 123) = 2.21$, $p > .05$.

Table 19 also shows the mean Recalled Childhood Gender Identity/Gender Role Questionnaire Factor 1 score of the participants as a function of DSM diagnostic status for GID in childhood. With age and social class covaried, the threshold participants recalled, on average, more cross-gender behavior in childhood than the participants who were

³² The males in Singh et al. (2010) were significantly older than the participants in the present study.

subthreshold for a diagnosis of GID. However, the difference only approached significance $F(1, 70) = 3.53, p = .06$.

3.9.2.1 Recalled Childhood Sex-Typed Behavior as a Function of Group

On the Recalled Childhood Gender Identity/Gender Role Questionnaire (see Table 18), there was a significant main effect for Group, $F(2, 67) = 30.20, p < .001$, partial $\eta^2 = .51$. Post-hoc analyses revealed that all three pair-wise group comparisons were significant ($ps < .001$). The bisexual/homosexual persisters recalled, on average, significantly more cross-gender behavior during childhood than both the bisexual/homosexual desisters and the heterosexual desisters. The bisexual/homosexual desisters, in turn, recalled significantly more cross-gender behavior in childhood than did the heterosexual desisters.

Across the entire group of 139 participants, there were 71 cases where both the gender dysphoria score and the Recalled Childhood Gender Identity/Gender Role Questionnaire score was available. Based on these cases, the correlation between the gender dysphoria score and the Recalled Childhood Gender Identity/Gender Role Questionnaire was significant, $r(71) = -.65, p < .001$.

3.9.2.2 Recalled Childhood Sex-Typed Behavior and Childhood-Sex-Typed Behavior

Across the entire sample, the relationship between recalled childhood sex-typed behavior (assessed at follow-up) and childhood sex-typed behavior at the original assessment was examined. Participants' score on the Recalled Childhood Gender Identity/Gender Role Questionnaire was correlated with their score on seven measures of childhood sex-typed behaviors (see Table 14 for a listing of these measures). There were four significant correlations. Participants' recollections of their sex-typed behaviors was significantly correlated with parent report of their childhood cross-gender behaviors on the

Gender Identity Questionnaire for Children, $r(65) = .35, p < .01$. The Recalled Childhood Gender Identity/Gender Role Questionnaire also correlated significantly with free play, $r(65) = -.35, p < .01$, cross-sex peer choice on the Playmate and Play Style Preferences Structured Interview, $r(33) = -.39, p < .05$, and cross-sex toy choice on the Playmate and Play Style Preferences Structured Interview, $r(33) = -.44, p < .01$. There was no significant correlation between the Recalled Childhood Gender Identity/Gender Role Questionnaire and the Gender Identity Interview, temperament/activity level, and difference between cross-sex and same-sex responses on the Rorschach ($ps > .05$).³³

3.9.3 Sexual Orientation

The results for sexual orientation in fantasy are presented first, followed by sexual orientation in behavior.

3.9.3.1 Sexual Orientation in Fantasy

For the Erotic Response and Orientation Scale (EROS), a concurrent measure of sexual orientation in fantasy, a mean homoerotic fantasy score was computed for the 8 items pertaining to attraction to men and a mean heteroerotic fantasy score was computed for the 8 items pertaining to attraction to women. A 3 (group) x 2 (EROS: homoerotic vs. heteroerotic) repeated measures ANCOVA revealed a significant interaction, Wilks' Lambda = .42, $F(2, 92) = 64.30, p < .001$, partial $\eta^2 = .58$, which was decomposed with post hoc contrasts. Across the groups, the heterosexual desisters reported, on average, significantly more heteroerotic fantasy than both the bisexual/homosexual persisters ($p < .001$) and the bisexual/homosexual desisters ($p < .001$). Furthermore, the bisexual/homosexual desisters reported, on average, significantly more heteroerotic fantasy than the bisexual/homosexual persisters ($p =$

³³ These analyses were repeated using partial correlations in which age at assessment, age at follow-up, and follow-up interval were controlled for. The pattern of significant findings did not change.

.036). In contrast, the heterosexual desisters reported, on average, significantly less homoerotic fantasy than both the bisexual/homosexual persisters and the bisexual/homosexual desisters (both $ps < .001$). The bisexual/homosexual persisters and bisexual/homosexual desisters did not differ significantly from each other on mean homoerotic fantasy ($p > .05$). Within groups, the bisexual/homosexual persisters reported, on average, significantly more homoerotic than heteroerotic fantasy ($p < .001$); the bisexual/homosexual desisters also reported, on average, significantly more homoerotic than heteroerotic fantasy ($p < .001$). In contrast, the heterosexual desisters reported, on average, significantly more heteroerotic than homoerotic fantasy ($p < .001$).

I also classified patients dichotomously as either “homosexual” or “non-homosexual” based on an EROS difference score (Homoerotic – Heteroerotic). If the difference score was > 0 , the participant was classified as homosexual in relation to their birth sex. If the difference score was ≤ 0 , then the patient was classified as non-homosexual (i.e., heterosexual, bisexual, or asexual). Based on this criterion (Table 20), 93.3% of the bisexual/homosexual persisters and 80.0% of the bisexual/homosexual desisters were classified as homosexual; in contrast, none of the heterosexual desisters were classified as homosexual.

3.9.3.2 *Sexual Orientation in Behavior*

For the Sexual History Questionnaire, a measure of concurrent sexual orientation in behavior, a mean homoerotic behavior score was computed for the 10 items pertaining to attraction to men and a mean heteroerotic behavior score was also computed for the 10 items pertaining to attraction to women. A 3 (group) x 2 (Sexual History Questionnaire: homoerotic vs. heteroerotic) repeated measure ANCOVA revealed a

Table 20

Sexual Orientation in Fantasy and Behavior on EROS and SHQ

Variable		Persisters Bisexual/ Homosexual (<i>n</i> = 15)	Desisters Bisexual/ Homosexual (<i>n</i> = 50)	Desisters Heterosexual (<i>n</i> = 37)
EROS	% Homosexual ^a	93.3	80.0	0
	N	14	40	0
SHQ	% Homosexual ^b	93.3	64.0	0
	N	14	32	0

Note. EROS = Erotic Response and Orientation Scale; SHQ = Sexual History Questionnaire.

^aEROS difference score (Homoerotic – Heteroerotic) > 0.

^bSHQ difference score (Homoerotic – Heteroerotic) > 0.

significant interaction, Wilks' lambda = .63, $F(2, 91) = 26.40$, $p < .001$, partial $\eta^2 = .37$, which was decomposed with post hoc contrasts.

Across groups, there was no significant difference on heterosexual behavior (all $ps > .05$). However, the post hoc contrast between the bisexual/homosexual persisters and the heterosexual desisters approached significance ($p = .08$), with the latter group reporting more heterosexual behavior. In contrast, all three post hoc comparisons on homosexual behavior were significant. The heterosexual desisters reported, on average, significantly less homoerotic behavior than both the bisexual/homosexual persisters and the bisexual/homosexual desisters (both $ps < .001$). The bisexual/homosexual persisters reported, on average, significantly more homoerotic behavior than the bisexual/homosexual desisters ($p < .01$). Within groups, the bisexual/homosexual persisters reported, on average, significantly more homoerotic than heteroerotic behavior ($p < .001$); the bisexual/homosexual desisters

also reported, on average, significantly more homoerotic than heteroerotic behavior ($p = .001$). In contrast, the heterosexual desisters reported, on average, significantly more heteroerotic than homoerotic behavior ($p < .001$).

I also classified patients dichotomously as either “homosexual” or “non-homosexual” based on the Sexual History Questionnaire difference score (Homoerotic – Heteroerotic). If the difference score was > 0 , the participant was classified as homosexual in relation to their birth sex. If the difference score was ≤ 0 , then the patient was classified as non-homosexual (i.e., heterosexual, bisexual, or asexual). Based on this criterion (Table 20), 93.3% of the bisexual/homosexual persisters and 64.0% of bisexual/homosexual desisters were classified as homosexual; in contrast, none of the heterosexual desisters were classified as homosexual.

3.9.4 Parent Report of Concurrent Gender Role

On the parent report Gender Identity/Gender Role Questionnaire for Adolescents, a measure of concurrent gender role behaviors, there was a significant main effect for Group, $F(2, 86) = 23.28, p < .001$, partial $\eta^2 = .37$ (Table 18). Post-hoc analyses revealed that all three pair-wise group comparisons were significant (all $ps < .001$). The bisexual/homosexual persisters had, on average, more cross-gender behavior than both the bisexual/homosexual desisters and the heterosexual desisters. The bisexual/homosexual desisters had, on average, significantly more cross-gender compared to the heterosexual desisters.

Across the entire sample, the relationship between parent report of concurrent gender role behaviors and childhood sex-typed behaviors was examined. Participants’ score on the Gender Identity/Gender Role Questionnaire for Adolescents was correlated with their score on nine measures of sex-typed behaviors (see Table 16 for a listing of these measures). There was only one significant correlation. Participants’ parent report of concurrent gender role

behavior was significantly correlated with parent-report of their child's cross-gender behavior on the Gender Identity Questionnaire for Children, $r(46) = -.39, p < .01$.

3.10 Behavior Problems at Follow-up

Table 21 shows the correlation coefficients on the behavior measures in childhood and at follow-up. Cohen's (1988) criteria were used to evaluate the magnitude of the correlations: small ($r = .10-.29$), medium ($r = .30-.49$) or large ($r \geq .50$).

Maternal ratings in childhood was significantly correlated with maternal ratings at follow-up for Internalizing problems ($r[90] = .36, p < .001$), Externalizing problems ($r[90] = .36, p < .001$), and Total problems ($r[90] = .43, p < .001$). Maternal ratings at follow-up was significantly correlated with participant self-report at follow-up for Internalizing problems ($r[87] = .37, p < .001$), Externalizing problems ($r[87] = .49, p < .001$), and Total problems ($r[87] = .47, p < .001$). None of correlations between maternal ratings in childhood and participant self-report at follow-up were significant ($ps > .05$).

3.10.1 Behavior Problems at Follow-up as a Function of Gender Identity and Sexual Orientation: Maternal-Report

Table 17 shows the maternal ratings on the CBCL/ABCL at follow-up as a function of group. ANCOVAs (with age at assessment, IQ in childhood, social class, age at follow-up, IQ at follow-up, and marital status³⁴ co-varied) were used to examine whether the groups differed on any of the reported follow-up variables (Internalizing T score, Externalizing T score, Total T score). One-way ANCOVAs for Group revealed no significant group differences on maternal ratings of Internalizing, Externalizing, and Total Problems at follow-up. Table 17 also shows the percentage of participants in each group who fell within the clinical range (T score $> 90^{\text{th}}$ percentile) according to their Internalizing, Externalizing, and

³⁴ The ANCOVA model was adjusted to accommodate a categorical covariate.

Table 21

Correlations between Behavior Problems in Childhood (CBCL) and Follow-up (YSR/ASR, CBCL/ABCL)

Measure	1	2	3	4	5	6	7	8	9
1 CBCL Internalizing <i>T</i>	-	.79***	.82***	.04	.03	.08	.36***	.27**	.39***
2 CBCL Externalizing <i>T</i>		-	.89***	.03	.09	.11	.30**	.36***	.40***
3 CBCL Total <i>T</i>			-	.02	.07	.10	.34**	.35**	.43***
4 Follow-up Self-Report Internalizing <i>T</i>				-	.69***	.89***	.37**	.35**	.37**
5 Follow-up Self-Report Externalizing <i>T</i>					-	.90***	.35**	.49***	.41***
6 Follow-up Self-Report Total <i>T</i>						-	.40***	.49***	.47***
7 Follow-up Parent-Report Internalizing <i>T</i>							-	.71***	.89***
8 Follow-up Parent-Report Externalizing <i>T</i>								-	.90***
9 Follow-up Parent-Report Total <i>T</i>									-

Note. CBCL at childhood assessment, $n = 124$. YSR/ASR self report at follow-up, $n = 100$.

CBCL/ABCL parent-report at follow-up, $n = 90$.

* $p < .05$, ** $p < .01$, *** $p < .001$.

Total *T* scores obtained from maternal ratings. For the bisexual/homosexual persisters, 23.1%-38.5% fell within the clinical range depending on the specific variable used in classification (i.e., Internalizing *T*, Externalizing *T*, or Total *T*); for the bisexual/homosexual desisters, 20.5%-36.4% fell in the clinical range; for the heterosexual desisters, 15.2%-27.3% fell in the clinical range. These percentages did not differ significantly (see Table 17, footnotes e, f, and g).

3.10.2 Behavior Problems at Follow-up as a Function of Gender Identity and Sexual Orientation: Self-Report

ANCOVAs (with age at assessment, IQ in childhood, social class, age at follow-up, IQ at follow-up, and marital status³⁵ co-varied) were conducted to examine whether the groups differed on participant self-report of their behavior problems on the YSR/ASR at follow-up. Table 17 shows participants' self-report ratings on the YSR/ASR as a function of group. There was a significant main effect for Group on Internalizing *T* score, $F(2, 99) = 5.05, p = .008$, but not for Externalizing *T* score, $F(2, 99) < 1$. The ANCOVA for Total *T* score approached significance, $F(2, 99) = 2.60, p = .08$. For Internalizing *T* score, post hoc analyses using *lmatrix* commands revealed two significant pairwise comparisons. The heterosexual desisters had, on average, a lower Internalizing *T* score than both the bisexual/homosexual persisters and the bisexual/homosexual desisters (both $ps < .05$), who did not differ from each other ($p > .05$).

Table 17 also shows the percentage of participants in each group who fell within the clinical range (*T* score $> 90^{\text{th}}$ percentile) according to their self-report of Internalizing, Externalizing, and Total Problems. For the bisexual/homosexual persisters, 46.7%-53.3% fell within the clinical range depending on whether they were classified according to their Internalizing *T* score, Externalizing *T* Score, or Total *T* score; for the bisexual/homosexual desisters, 18.0%-24.0% fell in the clinical range; for the heterosexual desisters, 5.6%-11.1% fell within the clinical range. These percentages were significantly different (ps ranged from .001-.017, refer to Table 17 footnotes h, i, and j.). For Internalizing *T* score, post hoc analyses showed that a greater proportion of the bisexual/homosexual persisters fell within the clinical range compared to the heterosexual desisters, $\chi^2(1, N = 51) = 5.95, p = .015$. The pairwise

³⁵ The ANCOVA model was adjusted to accommodate a categorical covariate.

comparisons between the heterosexual desisters and bisexual/homosexual desisters and between the bisexual/homosexual persisters and bisexual/homosexual desisters were not significant (both $ps > .05$). For Externalizing T score, there were two significant pairwise comparisons: a smaller proportion of the heterosexual desisters fell within the clinical range compared to the bisexual/homosexual desisters, $\chi^2(1, N = 86) = 3.96, p = .047$, and to the bisexual/homosexual persisters, $\chi^2(1, N = 51) = 12.45, p < .001$. For the Total T score, only one comparison was significant: a greater proportion of the bisexual/homosexual persisters fell within the clinical range compared to the heterosexual desisters, $\chi^2(1, N = 51) = 5.95, p = .015$.

For comparative purposes, the percentage of participants from each group who fell within the clinical range based on Total T score can be compared to data on referred and nonreferred boys from the YSR standardization samples. In the YSR standardization sample, 30% and 9% of referred and nonreferred boys, respectively, fell within the clinical range based on Total T score. Chi-square analyses revealed that the group differences on the YSR were significant, $\chi^2(4) = 34.53, p < .001$. Pair-wise comparisons revealed that the percentage of bisexual/homosexual persisters whose total score fell within the clinical range was considerably higher than that in nonreferred boys (both $p < .001$) but comparable to referred boys ($p > .05$). The percentage of bisexual/homosexual desisters whose total score was in the clinical range was comparable to that in referred and nonreferred youth (both $ps > .05$). The percentage of heterosexual desisters whose total score was within the clinical range was lower than that in referred boys ($p = .01$) but comparable to that in nonreferred boys ($p > .05$).

3.11 Psychiatric Functioning at Follow-up

Table 22 shows the number of participants with no diagnosis, 1 diagnosis, 2 diagnoses, and 3 or more diagnoses on the Diagnostic Interview Schedule or Diagnostic Interview for Children and Adolescents.

Table 22

Number of Psychiatric Diagnoses at Follow-up on the DIS or DICA

Number of Diagnoses	N	%
0	40	37.0
1	25	23.1
2	18	16.7
3–9	25	23.2

Note. Data were only available for participants who completed the face-to-face interview. Of these, data were missing for 2 participants. The number of participants who received 3 or more diagnoses was low so these categories were collapsed. DIS = Diagnostic Interview Schedule (Administered to participants ≥ 18 years of age). DICA = Diagnostic Interview for Children and Adolescents (administered to participants < 18 years of age).

Of the 108 participants for whom data were available, 40 (37%) did not meet criteria for any diagnoses. The remaining 68 (63%) met criteria for at least 1 diagnosis. Of these, 25 (23.1%) met criteria for 1 diagnosis, 18 (16.7%) met criteria for 2 diagnoses, and the remaining 25 participants (23.2%) met criteria for 3 or more diagnoses (range, 3-9 diagnoses). Appendix L provides additional details on the number of diagnoses (and type, where applicable) for each participant.

3.11.1 Psychiatric Functioning at Follow-up as a Function of Gender Identity and Sexual Orientation

Of the 16 bisexual/homosexual persisters, data were available for 15 participants. Of these, 13 (86.6%) met criteria for one or more psychiatric diagnoses at follow-up (other than GID). Of the 66 bisexual/homosexual desisters, data were available for 51 participants. Of

these, 41 (80.3%) met criteria for one or more diagnoses. Of the 42 heterosexual desisters, data were available for 37 participants. Of these, 13 (35.1%) met criteria for one or more diagnoses.

Across the three groups, the number of participants administered the Diagnostic Interview Schedule versus the Diagnostic Interview for Children and Adolescents was not evenly distributed. As such, this rendered the total number of diagnoses for each participant potentially misleading. As an alternative to comparing the groups on the mean number of total diagnoses, a proportion score was calculated for each participant and this was used in group analyses. This score reflected the proportion of total possible diagnoses (17 for the Diagnostic Interview Schedule, 13 for the Diagnostic Interview for Children and Adolescents) that the participant obtained. Table 23 shows the means and SD for the proportion score for each group. For descriptive purposes only, Table 23 also shows the mean number of total diagnoses (and SD) according to gender identity and sexual orientation in fantasy.

A one-way ANCOVA (with age at assessment, IQ in childhood, social class, age at follow-up, IQ at follow-up, and marital status³⁶ co-varied) for Group was significant, $F(2, 101) = 6.97, p = .002$, partial $\eta^2 = .13$. Post hoc analyses using *lmatrix* commands revealed two significant contrasts. The heterosexual desisters, on average, met criteria for fewer diagnoses compared to the bisexual/homosexual desisters ($p = .001$) and to the bisexual/homosexual persisters ($p = .006$). The two bisexual/homosexual groups (i.e., the bisexual/homosexual persisters and the bisexual/homosexual desisters) did not differ significantly from each other.

³⁶ The ANCOVA model was adjusted to accommodate a categorical covariate.

Table 23

Psychiatric Functioning at Follow-up as a Function of Group

		Group			<i>F</i>	<i>p</i>	η^2
Variable		Persisters Bisexual/ Homosexual	Desisters Bisexual/ Homosexual	Desisters Heterosexual			
Number of Diagnoses (Proportion Score) ^a	M	.18	.17	.03	6.97	.002	.13
	SD	.13	.16	.05			
	N	14	51	37			
Total Number of Diagnoses	M	2.71	2.61	.49	-	-	-
	SD	2.27	2.41	.73			
	N	14	51	37			

Note. Dash (-) indicates that an ANCOVA was not conducted on this measure.

^aAbsolute range, .00-1.00.

3.12 Suicidality at Follow-up

3.12.1 Suicidality Questionnaire

Participants' experience of suicidality was assessed using the Suicidality Questionnaire. The Suicidality Questionnaire was added to the assessment protocol during the third (final) wave of data collection and, therefore, these data were missing for many participants. On this measure, participants reported suicidal thoughts and behaviors since the age of 13 years and in the 12 months preceding the follow-up assessment. Data were available for 48 participants (7 bisexual/homosexual persisters, 31 bisexual/homosexual desisters, and 10 heterosexual desisters). There was no significant difference between participants who completed the suicidality questionnaire and those who did not on any demographic variables (all *ps* > .05).

Regarding lifetime suicidal thinking/ideation, 8 (16.8%) participants reported that they had sometimes or often thought about suicide; 16 (33.3%) rarely thought about it. The remaining 24 (50%) had not thought about suicide since the age of 13 years. When asked about suicidal thinking in the 12 months preceding the follow-up assessment, 4 (8.3%) participants reported that they had sometimes thought of suicide; 3 (6.3%) rarely thought about it; and 41 (85.4%) never thought about it.

Of the 48 participants who completed the Suicidality Questionnaire, 15 (31.2%) reported that they attempted suicide since the age of 13 years. Of these 15 participants, 3 were bisexual/homosexual persisters, 11 were bisexual/homosexual desisters, and 1 was a heterosexual desister. Of the participants who attempted suicide, 9 reported that the suicide attempt was not related to their gender identity while the remaining 6 reported that it was related to their unhappiness about being a biological male. A one-way ANCOVA for Group was conducted to determine whether the three outcome groups differed significantly on number of suicide attempts since the age of 13.³⁷ The ANCOVA was significant, $F(2, 46) = 4.61, p = .016$, partial $\eta^2 = .20$. Post-hoc analyses using lmatrix command revealed one significant contrast. The bisexual/homosexual desisters reported, on average, a greater number of past suicide attempts compared to the heterosexual desisters ($p < .01$). There was no significant difference between the bisexual/homosexual persisters and the two desister groups (both $ps > .05$). The majority (95.8%) of participants had not attempted suicide over the past 12 months; however, 2 (4.2%) participants, both of whom were bisexual/homosexual desisters, reported that they attempted suicide once. Both participants reported that their suicide attempt was not at all related to their gender identity as male.

³⁷Group means for number of suicide attempts since the age of 13: Bisexual/homosexual persisters ($M = 1.43, SD = .53$); bisexual/homosexual desisters ($M = 1.43; SD = .73$); heterosexual desisters ($M = 1.10, SD = .32$).

3.12.2 Self-Report of Suicidality on the Youth Self-Report (YSR)/Adult Self-Report (ASR)

As many of the participants had not completed the Suicidality Questionnaire, suicidality was also measured by examining participants' responses on two relevant items on the YSR/ASR. These data were only available for participants who completed the face-to-face assessment.

Suicidal ideation was measured by examining participants' self-report on Item 91 of the YSR/ASR: "I think about killing myself." Items on the YSR and ASR are rated as 0 ("not true"), 1 ("somewhat or sometimes true") or 2 ("very true or often true), based on the 6 months preceding the follow-up assessment. Participants' response on this item was recoded dichotomously,³⁸ 0 = 0 and 1 or 2 = 1. As shown in Table 24, 46.7% of the bisexual/homosexual persisters, 19.1% of the bisexual/homosexual desisters, and 11.4% of the heterosexual desisters endorsed that they experienced suicidal ideation in the six months preceding the follow-up assessment. A chi-square analysis revealed that the three groups differed significantly on suicidal ideation, $\chi^2(2, N = 97) = 8.09, p = .018$. Pair-wise chi-square revealed one significant comparison: the heterosexual desisters were less likely to endorse this item than the bisexual/homosexual persisters ($p < .05$). The comparison between the bisexual/homosexual desisters and the bisexual/homosexual persisters approached significance ($p = .07$).

These results can be compared to standardization data for referred and nonreferred boys in the YSR and ASR standardization samples. In the YSR standardization sample³⁹, 20% and 7% of referred and nonreferred boys, respectively, endorsed Item 91. In the ASR

³⁸ Since the purpose of this analysis was to examine if there was a significant difference between the groups on whether suicidal thinking was endorsed or not, participants' response on Items 18 and 91 were recoded dichotomously where 0 indicated that the item was not endorsed and 1 indicated that the item was endorsed.

³⁹ Age range, 15-18.

Table 24

Suicidal Ideation and Behavior at Follow-up as a Function of Group

Variable	Group													
	Persisters							Desisters						
	Bisexual/Homosexual							Bisexual/Homosexual						
	0	%	1 or 2	N	%	1 or 2	N	0	%	1 or 2	N	%	1 or 2	N
	N							0						
YSR Suicidal Ideation	8	53.3	7	46.7	38	80.9	9	31	88.6	4	11.4	8.09	8.09	.018
YSR Suicidal Behavior	9	60.0	6	40.0	45	95.7	2	32	91.4	3	8.6	14.87	14.87	.001
CBCL Suicidal Ideation	10	76.9	3	23.1	42	93.3	3	28	84.8	5	15.2	3.01	3.01	ns
CBCL Suicidal Behavior	11	84.6	2	15.4	44	97.8	1	30	90.9	3	9.1	3.36	3.36	ns

Note. Suicidal ideation and behavior were assessed using Item 91 and Item18 of the YSR/ASR and CBCL/ABCL, respectively.

standardization sample⁴⁰, 28% and 3% of referred and nonreferred boys, respectively, endorsed item 91. Chi-square analyses revealed that the group differences on the YSR and ASR were significant, $\chi^2(4) = 25.46, p < .001$ and $\chi^2(4) = 59.83, p < .001$, respectively. Pair-wise comparisons revealed that, the bisexual/homosexual persisters were significantly more likely to endorse Item 91 compared to the referred and nonreferred boys in the YSR standardization sample ($p = .01$ and $p < .001$, respectively). The bisexual/homosexual persisters were significantly more likely to endorse Item 91 compared to the nonreferred boys in the ASR standardization sample ($p < .001$) but were comparable to the referred boys. The bisexual/homosexual desisters were more likely to endorse Item 91 compared to the nonreferred boys and in the YSR standardization sample ($p = .01$) and the ASR standardization sample ($p < .001$). The bisexual/homosexual desisters were comparable to the referred boys in both the YSR and ASR standardization samples (both $ps > .05$). The heterosexual desisters were significantly more likely than the nonreferred boys in the ASR standardization sample to endorse Item 91 ($p = .01$), but less likely than the referred boys ($p = .03$). However, the heterosexual desisters were comparable to the referred and nonreferred boys in the YSR standardization sample (both $ps > .05$).

Suicidal behavior was measured by examining participants' self-report on Item 18 of the YSR/ASR: "I deliberately try to hurt or kill myself." Similar to the analysis on Item 91 of the YSR/ASR, participants' responses were recoded dichotomously, 0 = 0 and 1 or 2 = 1. As summarized in Table 24, 40% of the bisexual/homosexual persisters, 4.3% of the bisexual/homosexual desisters, and 8.6% of the heterosexual desisters reported that they engaged in suicidal behavior in the six months preceding the follow-up assessment. A chi-square analysis revealed that these group differences were significant, $\chi^2(2, N = 97) = 14.87, p =$

⁴⁰ Age range, 18-59.

.001. Pair-wise chi-square analyses revealed two significant comparisons. The bisexual/homosexual persisters were more likely to endorse this item than the bisexual/homosexual desisters and the heterosexual desisters (both $ps < .05$).

These results can be compared to standardization data for referred and nonreferred boys in the YSR and ASR standardization samples. In the YSR standardization sample⁴¹, 11% and 2% of referred and nonreferred boys, respectively, endorsed Item 18. In the ASR standardization sample⁴², 20% and 7% of referred and nonreferred boys, respectively, endorsed Item 18. Chi-square analyses revealed that the group differences on the ASR and YSR were significant, $\chi^2(4) = 40.93, p < .001$ and $\chi^2(4) = 28.62, p < .001$, respectively. The results of comparisons varied depending on the standardization sample used in the comparison. The bisexual/homosexual persisters were significantly more likely to endorse this item compared to the referred and nonreferred boys in the YSR standardization sample (both $ps < .001$) and the ASR standardization sample ($p = .006$ and $p < .001$, respectively). The bisexual/homosexual desisters were comparable to the referred and nonreferred boys in the YSR standardization sample (both $ps > .05$). The bisexual/homosexual desisters were less likely to endorse Item 18 compared to referred boys in the ASR standardization sample ($p = .01$) but were comparable to the nonreferred boys. The heterosexual desisters were more likely to endorse this item compared to the nonreferred boys in the YSR ($p = .005$), but were comparable to the referred boys ($p > .05$). The heterosexual desisters were comparable to the referred and nonreferred boys in the ASR standardization sample (both $ps > .05$).

Participants' responses on Item 18 and Item 91 were significantly correlated, $r(97) = .68, p < .001$.

⁴¹ Age range, 15-18.

⁴² Age range, 18-59.

3.12.3 Parent-Report of Suicidality on the Child Behavioral Checklist (CBCL)/Adult Behavior Checklist (ABCL)

Maternal report of participants' suicidality was also examined using the CBCL/ABCL. Maternal report of suicidal ideation was measured on Item 91 ("Talking about killing self") and suicidal behavior was measured on Item 18 ("Deliberately harms self or attempts suicide"). Similar to the coding system utilized for YSR/ASR suicidality items, maternal responses on Items 18 and 91 were recoded dichotomously as 0 = 0 and 1 or 2 = 1. A chi-square analysis revealed that the three groups did not differ significantly on maternal reports of suicidal ideation or suicidal behavior, $ps > .05$ (Table 24). Across all participants, the correlation between Item 18 and Item 91 on the CBCL/ABCL was significant, $r(91) = .53, p < .001$.

The extent of agreement between self-report and parent-report of suicidality was examined. For suicidal behavior, the correlation was not significant, $p > .05$. In contrast, the correlation between self and maternal report of suicidal ideation was significant, $r(89) = .38, p < .001$.

3.13 Victimization Experiences

The purpose of the victimization questionnaire was to gain a greater understanding of participants' experiences of victimization related to their gender identity and gender role. The Victimization Survey was added to the assessment protocol during the third (final) wave of data collection and, therefore, these data were missing for participants who were assessed prior to 2008. On this measure, participants rated the frequency with which they experienced three types of verbal victimization and four types of physical victimization since the age of 13 years (also referred to as lifetime victimization) and in the 12 months preceding the

follow-up assessment. Data were available for 48 participants (7 bisexual/homosexual persisters, 31 bisexual/homosexual desisters, and 10 heterosexual desisters). There was no significant difference between participants for whom victimization data were available and those where data were not available on any demographic variables (all $ps > .05$).

3.13.1 Descriptive Victimization Experiences for the Entire Sample

Of the 48 participants for whom data were available, 30 (62.5%) had experienced some type of victimization since the age of 13-years-old/in their lifetime related to their gender identity.⁴³

Of the 48 participants, 29 (60.4%) had experienced some type of verbal victimization (e.g., verbal insults, threats to tell others about gender identity, threat of violence) in their lifetime (Table 25). Verbal insults were experienced more often than both threats to tell others about their gender identity and threat of a physical attack; 29 (60.4%) participants had experienced a verbal insult related to their gender identity at least once in their life, 16 (33.3%) experienced a threat of violence, and 10 (20.8%) were threatened by others to have their gender identity disclosed.

As shown in Table 25, for all types of verbal victimization (insults and threats), it was more common for participants to have experienced 3 or more episodes of victimization than a single episode. Based on the 12 months prior to the follow-up assessment, 19 (39.6%) participants had experienced at least one type of verbal victimization. Of the 48 participants, 19 (39.6%) had experienced verbal insults in the past 12 months, 8 (16.7%) experience a threat of violence, and 5 (10.5%) were threatened by others to have their gender identity disclosed.

⁴³ For the participants who experienced victimization, they were bullied in regard to their gender role behaviors and being effeminate, rather than about their gender identity per se.

Table 25
Gender Identity-Related Victimization

Type of victimization	Frequency of Victimization											
	Past 12 months						Since the age of 13 years/lifetime					
	0		1		2		≥3		0		1	
	N	%	N	%	N	%	N	%	N	%	N	%
<u>Verbal victimization</u>												
Verbal insults	29	60.4	0	0	7	14.6	12	25.0	19	39.6	3	6.3
Threats of violence	43	89.6	3	6.3	2	4.2	0	0	38	79.2	2	4.2
Threat of disclosure	40	83.3	3	6.3	4	8.3	1	2.1	32	66.7	5	10.4
<u>Physical victimization</u>												
Object thrown	38	79.2	8	16.7	1	2.1	1	2.1	28	59.3	6	12.5
Physical assault	44	91.7	4	8.3	0	0	0	0	36	75.0	6	12.5
Threat with a weapon	47	97.9	0	0	0	0	1	2.1	42	87.5	4	8.3
Sexual assault	47	97.9	1	2.1	0	0	0	0	44	91.7	3	6.3

Note. Data were available for 48 participants (7 bisexual/homosexual persisters, 31 bisexual/homosexual desisters, and 10 heterosexual desisters).

For frequency of Victimization: 0 = Never, 1 = Once, 2 = Twice, ≥3 = 3 or more times

Of the 48 participants who completed the Victimization Survey, 22 (45.8%) had experienced at least one type of physical victimization (objects thrown at them, being punched/ kicked/beaten, threatened with a weapon, sexually attacked) since the age of 13-years-old (Table 25). The most commonly experienced type of physical victimization was having an object thrown at them; 20 (41.7%) participants had an object thrown at them at least once, 12 (25%) had been physically attacked (punched, beaten, kicked), 6 (22.5%) were threatened with weapons, and 4 (8.4%) were sexually assaulted. Across the four types of physical victimization reported on, a report of one episode of physical victimization was generally more common than a report of multiple episodes. Based on the 12 months prior to the follow-up assessment, 11 (22.9%) participants had experienced at least one type of physical victimization. Of the 48 participants, 10 (20.8%) had an object thrown at them, 4 (8.3%) were physically attacked, 1 (2.1%) was threatened with weapons, and 1 (2.1%) was sexually attacked.

Visual inspection of the data with regard to the location of the victimization incidents revealed that they most commonly occurred at school or in the neighborhood. The most common assailants were strangers and peers.

3.13.2 Victimization Experiences as a Function of Sexual Orientation in Fantasy

For each participant, a mean score was calculated for verbal victimization, physical victimization, and overall victimization (verbal and physical combined) based on the frequency of occurrence of victimization experiences in the past 12 months. Mean scores were also calculated for frequency of victimization since the age of 13 years. In total, six mean scores were calculated for each participant (Table 26).

Table 26

Mean Frequency of Victimization as a Function of Gender Identity and Sexual Orientation in Fantasy

		Group			<i>F</i>	<i>p</i>	η ²
		Persisters Bisexual/ Homosexual (<i>n</i> = 7)	Desisters Bisexual/ Homosexual (<i>n</i> = 30)	Desisters Heterosexual (<i>n</i> = 10)			
Variable							
<u>Since the age of 13 years</u>							
Verbal Victimization ^a	M	1.76	.92	.47	3.46	.042	.15
	SD	1.07	1.05	.61			
Physical Victimization ^b	M	1.07	.37	.18	4.60	.016	.20
	SD	.83	.57	.33			
Overall Victimization ^c	M	1.37	.60	.30	4.25	.022	.18
	SD	.87	.75	.42			
<u>Past 12 months</u>							
Verbal Victimization ^a	M	1.38	.39	.23	6.38	.004	.25
	SD	.91	.58	.50			
Physical Victimization ^b	M	.50	.06	.00	7.21	.002	.27
	SD	.72	.11	.00			
Overall Victimization ^c	M	.88	.20	.10	8.89	.001	.31
	SD	.76	.27	.21			

Note. Absolute range for mean frequency scores, 0-4.^aCalculated as: (sum of frequency of each type of verbal victimization)/3^bCalculated as: (sum of frequency of each type of physical victimization)/4^cCalculated as: (sum of frequency of all type of verbal victimization)/7

A series of one-way ANCOVAs (with age at assessment, age at follow-up, IQ in childhood, IQ at follow-up, social class, and marital status covaried) were conducted to determine whether the three outcome groups differed on mean frequency for verbal, physical and total victimization experiences since the age of 13 years. There was a significant main effect for Group on all three variables. The significant ANCOVAs were followed up with post-hoc analyses using lmatrix commands. For mean verbal victimization since the age of 13 years, there was one significant post hoc contrast: the bisexual/homosexual persisters had experienced, on average, significantly more victimization than the heterosexual desisters ($p < .05$). For mean physical victimization since the age of 13 years, the bisexual/homosexual persisters had experienced, on average, significantly more physical victimization than both the bisexual/homosexual desisters and the heterosexual desisters (both $ps > .05$). Not surprisingly, the groups also differed on their mean overall victimization scores for which two contrasts were significant: the bisexual/homosexual persisters reported, on average, significantly more victimization than both the bisexual/homosexual desisters ($p = .05$) and the heterosexual desisters ($p = .006$).

The above-described ANCOVAs were repeated to examine whether the groups differed in their victimization experiences (verbal, physical, and total) based on the 12 months preceding the follow-up interview. There was a significant main effect for Group on all three measures. The significant ANCOVAs were followed up with post-hoc analyses using lmatrix commands. For mean verbal victimization, mean physical victimization, and mean overall victimization in the 12 months preceding the follow-up assessment, bisexual/homosexual persisters reported, on average, significantly more victimization than both the bisexual/homosexual desisters and the heterosexual desisters (all $ps < .01$). The bisexual/

homosexual desisters and heterosexual desisters did not significantly differ on any of the measures.

3.13.3 Victimization and Mental Health

Although not a focus of the follow-up study, the relationship between participants' overall mean score on the victimization survey and their mental health functioning was examined. Participants' Internalizing *T* score, Externalizing *T* score, and Total Problems *T* score on the Youth Self Report (YSR) or Adult Self Report (ASR) at follow-up was correlated with their mean overall victimization score for the past 12 months.⁴⁴ Participants' overall victimization score was significantly correlated with their Externalizing *T* score, $r(46) = .34, p < .05$, and their Total Problems *T* Score, $r(46) = .33, p < .05$. The correlation between overall victimization score and Internalizing *T* score was not significant ($p > .05$).

The relationship between participants' mean overall victimization score and psychiatric diagnosis on the DIS/DICA, using the proportion score, was also examined. The correlation was not statistically significant, $r(47) = .20, p > .05$.

3.13.4 Victimization and Childhood Sex-Typed Behavior

Using the overall mean victimization scores, the relationship between participants' victimization experience and their childhood cross-gender behaviors was examined. Two sets of correlation analyses were conducted. First, participants' overall mean overall victimization score since the age of 13 years old (i.e., lifetime victimization) was correlated with their scores on the nine measures of childhood sex-typed behavior (see Table 16, for example, for a list of these measures). None of the correlations were significant (all $ps > .05$). Second, participants overall mean victimization score for the 12 months preceding the follow-up

⁴⁴ Since the YSR/ASR instructs participants to complete ratings based on the past 6 months and is, therefore, a reflection of current behavior problems, the mean overall victimization score for the past 12 months was used instead of lifetime (since the age of 13 years) victimization score.

assessment was correlated with their scores on the nine measures of childhood sex-typed behavior. There was only one significant correlation. Participants' victimization experiences were significantly correlated with parent-report of their childhood cross-gender behavior on the Gender Identity Questionnaire for Children, $r(46) = -.39, p < .01$.

3.13.5 Victimization and Parent-Report of Concurrent Gender Role Behavior

Participants overall mean victimization scores, for both lifetime (since the age of 13 years old) and the 12 months preceding the follow-up assessment was correlated with their score on the parent report Gender Identity/Gender Role Questionnaire for Adolescents, a measure of concurrent gender role behaviors. Participants' overall victimization score since the age of 13 years old was significantly correlated with their parents' report of their concurrent cross-gender behaviors, $r(42) = -.43, p < .01$. Similar results were obtained when the relationship between victimization in the 12 months preceding the follow-up assessment and parent-report of concurrent gender role was examined, $r(42) = -.59, p < .001$.

3.14 Comparisons with Other Follow-up Studies of boys with Gender Identity Disorder

3.14.1 Persistence Rates across Follow-up Studies of Boys with Gender Identity Disorder

Appendix M summarizes the persistence rate obtained in follow-up studies of boys with GID. Chi-square analysis revealed that the rates of persistent gender dysphoria across this study, Green (1987), and Wallien and Cohen-Kettenis (2008)⁴⁵ differed significantly, $\chi^2(2) = 14.30, p = .001$. Pair-wise comparisons showed a significant difference in persistence rates between the Green and Wallien and Cohen-Kettenis studies, $\chi^2(1) = 12.31, p < .001$, and between the present study and Wallien and Cohen-Kettenis, $\chi^2(1) = 7.22, p < .01$. The

⁴⁵ For the chi-square analysis, Wallien and Cohen-Kettenis' conservative persistence rate of 30% (i.e., calculated using only the 40 boys who were successfully traced a follow-up) was used. However, the chi-square analysis can also be conducted using the liberal persistence rate of 20.3%. Using this method, the difference in persistence rates across the three studies remained significant, $\chi^2(2) = 7.58, p = .02$.

comparison between the present study and Green approached significance, $\chi^2(1) = 3.73, p = .05$.

In Drummond et al.'s (2008) follow-up study of females with GID, 3 of the 25 participants were classified as persisters and the remaining 22 were desisters. When combined with the boys from the present study, there was a total of 20 persisters and 144 desisters and a persistence rate of 12.1% for the Toronto sample of boys and girls. Wallien and Cohen-Kettenis reported a persistence rate of 27% for their entire sample of males and females (21 persisters, 56 desisters). However, this calculation included 23 participants who could not be traced/contacted at follow-up but were assumed to be desisters. If a more conservative rate was calculated by excluding these 23 individuals, the persistence rate was 38.8%.

Chi-square analyses were used to compare the results of the combined Toronto sample with that of the combined males and females in the study by Wallien and Cohen-Kettenis (2008). Regardless of whether one used the conservative or liberal persistence rates from Wallien and Cohen-Kettenis' (2008) study, the rates of persistent gender dysphoria across the two clinics varied significantly, $\chi^2(1) = 18.96, p < .001$ and $\chi^2(1) = 8.43, p = .004$, respectively.

3.14.2 Threshold vs. Sub-threshold for Gender Identity Disorder in Childhood

In the present study, 88 (63.3%) of the 139 participants met diagnostic criteria for GID in childhood and the remaining 51 (36.7%) were subthreshold for the diagnosis. In the follow-up study by Wallien and Cohen-Kettenis (2008), 44 (74.5%) of the 59 boys met the full criteria for GID in childhood and the remaining 15 (25.5%) were sub-threshold for the

diagnosis. There was no significant difference in the percentage of boys who met full criteria for GID across the two studies, $\chi^2(1) = 2.36, p > .05$.

Chapter 4

Discussion

The present study represents the largest sample to date of clinic-referred boys with Gender Identity Disorder (GID) followed into adolescence and adulthood. The goals of the study were to examine gender identity, sexual orientation, and general psychiatric outcomes at follow-up. The findings related to gender identity and sexual orientation outcomes are discussed first followed by behavioral and psychiatric functioning. The key findings of the study were as follows: (1) the most common long-term outcome for boys with GID was desistence of gender dysphoria a with co-occurring homosexual sexual orientation, (2) the percentage of boys with persistent gender dysphoria was modest but significantly higher than the base rate of GID in the general population of biological males, (3) the percentage of boys who developed a bisexual/homosexual sexual orientation was much higher than the base rates of bisexual/homosexual sexual orientation in adult males in the general population, (4) social class and severity of cross-gender behavior in childhood were significant predictors of gender identity outcome at follow-up, (5) severity of childhood cross-gender behavior was a significant predictor of sexual orientation at follow-up, and (6) the heterosexual desisters reported significantly less behavioral and psychiatric difficulties compared to the bisexual/homosexual persisters and, to a lesser extent, the bisexual/homosexual desisters.

4.1 Representativeness of Sample and Participation Rate

Before providing an analysis of the findings, a comment on the representativeness of the sample should be made since differences between participants and non-participants can threaten the internal validity of a study (Campbell & Stanley, 1963). More than half of the patients who were identified as eligible to participate in the study were not recruited due to

time and financial constraints. Comparisons between the participants and these non-participants on demographic variables, behavior problems, and sex-typed behavior yielded minimal group differences: only 1 of the 17 comparisons was significant. At least based on these measures, the boys who participated in the study did not appear to differ substantially from those who were eligible to participate but were not recruited. The study participants were also compared to the cases where the families could not be traced and to the cases where either the parent or potential participant himself refused. The group differences were modest: one comparison (IQ) approached significance and a second comparison (marital status) was significant. Regarding the latter, participants were more likely to originate in a two-parent family while the cases that could not be traced were more likely to come from a family composition other than two parent (e.g., divorced, living with relatives). This finding is not surprising in the context of research which shows that single-parent families move considerably more often than two-parent families (e.g., McLanahan & Sandefur, 1994). Based on these comparisons, the 139 participants who agreed to participate appeared to be representative of the total pool of available patients and did not constitute a biased sample at follow-up.

The participation rate in this study was 95.9% of those who could be traced,⁴⁶ which is extremely high especially given that the mean duration between childhood assessment and follow-up was 12.88 years. This participation rate was higher than Drummond et al.'s (2008) follow-up study of girls (83.3%) but lower than Wallien and Cohen-Kettenis' (2008) follow-up study of boys and girls (100% of those who could be traced).

⁴⁶ In the present study, 19% of the potential participants could not be traced/contacted. The corresponding percentages of untraced participants in Drummond et al. (2008) and Wallien and Cohen-Kettenis (2008) were 8% and 30%, respectively.

4.2 Recollection of Childhood Cross-Gender Behaviors

In using a prospective design, this study was not reliant on participants' retrospective reporting of their childhood sex-typed behavior; however, the methodology did include a measure of recalled childhood cross-gender behaviors. While most of the participants in the present study no longer met criteria for GID, their recollections of sex-typed behavior in childhood was similar to the childhood recollections of biological males with GID assessed for the first time in adolescence and adulthood. Further, the participants recalled more cross-gender behaviors than adolescent and adult males referred for clinical reasons other than gender identity concerns (Singh et al., 2010).

Retrospective analysis of childhood sex-typed behaviors has been criticized on numerous grounds. In studies that examine the childhoods of adults with GID who present to specialized gender identity clinics, there may be a selection bias because they may not represent all individuals with GID (Drummond et al., 2008). For example, individuals who meet criteria for GID in childhood but show a desistence of their gender dysphoria in adolescence or adulthood would not be seen in a gender clinic because they no longer seek gender change. Thus, adults with GID seen in specialized gender clinics may be more representative of persisters rather than desisters. Beyond the potential for general distortion in memory than can occur with the passage of time (Hardt & Rutter, 2004), studies that have retrospectively examined the childhoods of heterosexual and homosexual adults have faced a more specific criticism related to selective retention/construction of experiences. It has been argued that the greater recollection of childhood cross-gender behaviors by homosexual compared to heterosexual adults reflects an attempt by these individuals to reconstruct a childhood that fits with current Western culture's belief that the childhoods of homosexual

adults is gender nonconforming (e.g., Gottschalk, 2003; Hoult, 1983/1984). In other words, they recall a childhood pattern of sex-typed behaviors that is aligned with beliefs about homosexual individuals so as to appear similar to them. Using this reasoning, one can also assert that children with GID who develop a heterosexual sexual orientation in adulthood might provide a narrative of their childhood sex-typed behaviors that is consistent with a masculine childhood, especially if their cross-gender behaviors caused them embarrassment or peer rejection.

Results of the present study did not support a retrospective distortion hypothesis. Participants' adult recollections of their childhood cross-gender behavior correlated significantly with four of seven measures of sex-typed behaviors in childhood, including one parent report and three self-report. Their recollections of how cross-gendered they were as children were comparable to their actual extent of cross-gendered behaviors in childhood. Thus, in contrast to the criticism of retrospective designs, the participants in this study, which included homosexual and heterosexual men, were generally not biased or selective in their recall. That participants recalled a cross-gendered childhood is consistent with a large body of research that has retrospectively examined childhood sex-typed behaviors of heterosexual and homosexual men (for a meta-analysis, see Bailey & Zucker, 1995), including studies that have utilized home videos (e.g., Rieger et al., 2008) and parent report (e.g., Bailey, Miller, & Willerman, 1993; Bailey, Nothnagel, & Wolfe, 1995; Bailey, Willerman, & Parks, 1991) in an attempt to reduce bias in recall. Given the findings across these studies, it is unlikely that inaccurate recollection of their childhood (i.e., retrospective distortion) accounts for the large and consistent differences in the childhood sex-typed behaviors between homosexual and heterosexual men.

4.3 GID Diagnosis in Childhood

The majority (63.3%) of boys in this study met complete diagnostic criteria for GID in childhood. The boys who did not meet the complete criteria showed some characteristics of cross-gender identification and some, based on the history provided by their parents, would have met full criteria had they been assessed earlier in development. Therefore, it is not likely that the subthreshold cases represented grossly false positives or inappropriate referrals. As an example, one participant who was assessed when he was 11-years-old and was subthreshold for GID exhibited a fair amount of cross-gender behavior (e.g., always chose female roles in role-play and usually used girls' clothing in dress-up play). He also showed some signs of cross-gender identification on psychological testing (e.g., his first drawn person on the Draw-a-Person task was a female, when asked if it would be better to be a boy or a girl he said "I don't know, in the middle I guess," and said he "sometimes" thinks he would like to be a girl). At the same time, he also had a moderate degree of same-gender role behavior, had not made explicit remarks of wanting to be a girl (according to parents), preferred boys and girls equally as peers, and played with male-typical and female-typical dolls with equal frequency. On psychological testing, this youngster indicated that there were some good things about being a boy but could not list any of them.

In the Toronto clinic, false positives almost never occur and about 70% of the children evaluated meet the full criteria for GID, which is similar to the percentage of threshold cases in the present follow-up sample (Zucker, 2010a). There appears to be variance in the cross-gender presentation of children referred to the Toronto clinic, with some meeting full criteria and some not, and this may be reflective of the apparent gender variance spectrum that is witnessed in this population of children. A number of adolescents who

present to the Toronto clinic seem to have only met the full diagnostic criteria for GID sometime in adolescence and, based on historical information provided, might have been subthreshold for GID in childhood.

Comparative analysis of the threshold and subthreshold cases revealed a number of significant differences between the groups. There was a relationship between age and diagnostic status in childhood. The boys who met full criteria for GID in childhood were significantly younger at the time of the childhood assessment than those who were subthreshold for the diagnosis. This finding could not be directly compared with other follow-up studies of boys with GID because requisite data from those studies were not available. However, there are clues that this finding represents a pattern in children with GID. Research using the DSM-III and DSM-III-R criteria found that younger children (under 7 years of age) were more likely to receive the diagnosis than were older children (Zucker, 1992). This appeared to be related to the fact that older children were less likely than younger children to verbalize their desire to be of the opposite gender, which was required for the diagnosis to be made. Fear of stigma and social desirability pressures may have been operating on these children. Clinical impression from assessing and treating older children with GID suggests that some children also attempt to conceal some of their cross-gender behaviors.

It is not surprising that, even with age at childhood assessment controlled for, the boys who met criteria for GID in childhood also showed more severe cross-gender behavior (or less same-gender behavior) on parent and self-report measures of sex-typed behavior than those who were subthreshold for the diagnosis. Similar differences were found between threshold and subthreshold cases of gender-referred children in the Netherlands: the

threshold cases were reported by parents as more severe in their cross-gendered behaviors compared to the subthreshold cases (Cohen-Kettenis et al., 2006). This difference between threshold and subthreshold cases may be reflecting a natural history of GID for some children whereby cross-gender identification and behaviors lessen over time. This is plausible given that some of the subthreshold cases would have met criteria for GID had they been assessed earlier in development. On the other hand, the subthreshold cases were, on average, older than the threshold cases; thus, differences in severity may be an artifact of social desirability, as discussed above. There are other factors that may also contribute to the relationship between age, diagnostic status, and symptom severity. For example, parental efforts to treat the condition even prior to the clinical assessment might have affected their child's gender identity development and resulted in a decrease in cross-gender behaviors and identification.

The subthreshold participants had more externalizing difficulties than the threshold participants. This may be related to the observed relationship between age and behavior problems in children with GID with older children showing more behavioral problems than younger children (Cohen-Kettenis et al., 2003). One hypothesis for this is that poorer peer relations in older children may be mediating the relationship between age and behavior problems (Zucker, 2005c).

4.4 Gender Identity and Sexual Orientation

4.4.1 Gender identity outcome

4.4.1.1 Rate of persistent gender dysphoria

The present study found that the majority of boys with GID showed desistence of their gender dysphoria when followed into adolescence and adulthood: 87.8% of the boys did

not report any distress about their gender identity at follow-up and were happy living as males. When persistence rate was examined as a function of GID diagnostic status (i.e., threshold vs. subthreshold) in childhood, there was no significant difference in the rates obtained for the two diagnostic groups. The two childhood diagnostic subgroups did not show significant differences in their developmental trajectories, at least in regard to persistence of gender dysphoria. In this study, the categorical diagnosis of GID itself was, therefore, not a good prognosticator of persistence/desistence of GID over time. This is in contrast to the follow-up study by Wallien and Cohen-Kettenis (2008) where all of the persisters met full criteria for GID in childhood compared to approximately half of the desisters; thus, persistence rate of gender dysphoria would have varied significantly for the threshold and sub-threshold groups.

Although across the present study and those by Green (1987) and Wallien and Cohen-Kettenis (2008) the majority of boys with GID no longer had GID in adolescence or adulthood, there was significant variability in the persistence rates obtained across the studies with a range of 2.3%-30%. The persistence rate of 12.2%⁴⁷ in the present study fell in between that obtained by Green and Wallien and Cohen-Kettenis, but was closer to the rate of 9.1% calculated by Zucker and Bradley (1995) in their summary of six follow-up studies of boys with GID. Possible explanations for this variability are discussed later.

4.4.2 Sexual orientation outcome.

4.4.2.1 Rate of Bisexual/Homosexual Sexual Orientation

Information on sexual fantasy and behaviors in the 12-month period preceding the follow-up assessment was obtained during a face-to-face semi-structured interview, from

⁴⁷ The persistence rate in the present study was almost identical to that obtained by Drummond et al. (2008)(12%) in their follow-up study of girls with GID.

which Kinsey ratings were assigned. The correlation between these two metrics of sexual orientation was very strong. One has to be cautious about the possibility that participants may have underreported a minority sexual orientation due to social desirability pressures; however, there was no significant relationship between sexual orientation and the propensity to give socially desirable responses on the measure of social desirability. It is recognized that these results do not directly confirm whether there was an underreporting of bisexual/homosexual fantasies and can only speak to group differences in social desirability.

Regarding sexual orientation in fantasy,⁴⁸ 63.6% of participants were classified as bisexual/homosexual at follow-up. The rate of a bisexual/homosexual outcome obtained in the present sample was similar to that obtained by Green (1987) and Wallien and Cohen-Kettenis (2008), 75% and 81%, respectively. Across these follow-up studies, the percentage of males with a bisexual/homosexual outcome was, therefore, greater than the percentage of males with a heterosexual outcome. These results were also similar to that obtained by Zucker and Bradley (1995) in their summary of six follow-up studies of boys with gender dysphoria: In the combined sample, 61.9% of males reported a bisexual/homosexual orientation at follow-up; however, it is unclear whether this was based on sexual fantasy or sexual behavior. In contrast to these results for biological males with gender dysphoria, all of the control boys in Green's (1987) study were classified as heterosexual at follow-up.

In contrast to the low rate of persistent GID in this study, the rate of bisexuality/homosexuality was very high and it represented the most common sexual orientation outcome for boys with GID. The percentage of participants in the present study who reported a bisexual/homosexual sexual orientation (63.6%) was substantially higher than the currently

⁴⁸ Although participants were interviewed about sexual fantasies and sexual behaviors, sexual orientation classification was based on their reported fantasies. The rationale for this approach was provided in the Results chapter.

accepted base rate of a homosexual sexual orientation in males of 3.1% (Laumann, Gagnon, Michael, & Michaels, 1994).

4.4.2.2 Sexual Orientation of Persisters

All but one of the persisters in the present study reported a bisexual/homosexual sexual orientation at follow-up. Only one persister reported a heterosexual sexual orientation. Similarly, in the follow-up studies summarized by Zucker and Bradley (1995) and in Green's (1987) study, all persisters reported a homosexual sexual orientation. In contrast, Wallien and Cohen-Kettenis (2008) reported that 83% of the male persisters in their sample were bisexual/homosexual. Wallien and Cohen-Kettenis hypothesized that some of the participants who reported a heterosexual sexual orientation may move toward a bisexual/homosexual sexual orientation later on. This was based on the observation that some participants reported different sexual orientations across the metrics of fantasy, behavior, and attraction. Thus, it may be possible that these individuals had not yet developed a consolidated sexual identity and may have been experimenting with their sexual identity. As well, Wallien and Cohen-Kettenis did not measure participants' propensity to give socially desirable responses; therefore, it remains unknown whether there was also an underreporting of bisexual/homosexual sexual orientation in their sample, a limitation that they noted.

4.4.2.3 Age and Sexual Orientation

Approximately one-third of the present sample reported a heterosexual sexual orientation and these males were significantly younger than the bisexual/homosexual participants at follow-up. The age difference between the desisting bisexual/homosexual participants and the desisting heterosexual participants may be related to the timing of

“coming out.”⁴⁹ Decades of research on “coming out” as gay or homosexual have shown that the period of first disclosure can range from mid-adolescence, around 16 or 17 years of age (e.g., D’Augelli, Hersherberger, & Pilkington, 1998; Grov, Bimbi, Nanin, & Parson, 2006; Newman & Muzzonigro, 1993), to late adolescence and early 20s (e.g., Barber, 2000; Herek, Cogan, Gillis, & Glunt, 1998; McDonald, 1982; Savin-Williams, 1998; Savin-Williams & Ream, 2003). It is possible that some of the heterosexual males, if followed up later in their adult life, will continue to identify as heterosexual while others may disclose a bisexual or homosexual identity. Indeed, the literature on sexual identity development of gay and bisexual youth has shown that there can be change in identity over time and this may be related to the stages of the “coming out” process (e.g., Lever, 1994; Rosario, Schrimshaw, & Hunter, 2008; Rosario, Schrimshaw, Hunter, & Braun, 2006; Stokes, Damon, & McKirnan, 1997). In Green’s (1987) study, which included multiple follow-up assessments between childhood and adulthood, there was a shifting in sexual identity over the course of follow-up for some participants (e.g., one male identified as heterosexual at age 15, bisexual at age 16, and homosexual at age 20). We do not know, however, what factors contributed to the change in reported sexual identity. It is unclear, for example, if this shift represented a bona fide change in the participants’ sexual identity or whether there may have been other factors, such as social desirability, which rendered the participant unwilling to disclose their homosexual sexual identity as the earlier assessment conducted when he was 15-years-old.

⁴⁹ “Coming out” is the process of sexual orientation identity development for gay, lesbian, and bisexual individuals and is sometimes used synonymously with the disclosure of sexual identity to others (e.g., Heatherington & Lavner, 2008). While there is individual variation, stage theories suggest that the process generally begins with awareness of same-sex attraction, followed by same-sex, and sometimes opposite-sex, sexual experience and gradual acceptance and integration of a gay/lesbian/bisexual identity. Coming out is generally thought to culminate with disclosure (Floyd & Bakeman, 2006; Martin, 1991; McDonald, 1982).

4.4.3 Multiple Long-term Psychosexual Outcomes for Boys with GID

With gender identity and sexual orientation outcomes combined, there were diverse developmental outcomes for boys with GID, three of which were primary: (1) persistence of GID with a bisexual/homosexual sexual orientation, (2) desistence of GID with a bisexual/homosexual sexual orientation, and (3) desistence of GID with a heterosexual sexual orientation. The fourth outcome, persistence of GID with heterosexual sexual orientation, was least common and seen in only one participant. Most of the boys in this study no longer experienced gender dysphoria when followed into adolescence and adulthood, which is consistent with findings from previous follow-up studies. Thus, GID in childhood appears to be more strongly associated with a desisting homosexual outcome rather than a transsexual outcome. The observed variation in the long-term psychosexual outcome of boys with GID suggests that biological reductionist accounts of psychosexual development are too simplistic. These results did not support the view that GID in childhood is isomorphic with homosexuality in adulthood. Predictors of this observed variability are subsequently discussed.

4.5 Predictors of Gender Identity Outcome

The long-term psychosexual outcome for boys with GID can be encapsulated by the principle of multifinality from the developmental psychopathology literature (i.e., multiple long-term outcomes from a common starting point in childhood—gender dysphoria). That there are multiple long-term outcomes for boys with GID raises a number of questions, one of which is whether there are childhood features that distinguish between the boys who will persist in their gender dysphoria from those who will desist. In the present study, the sample

size was large enough to examine whether demographic variables, sex-typed behavior, or behavior problems in childhood could predict group outcome at follow-up.

4.5.1 Demographic Predictors of Gender Identity Outcome

Of the childhood demographic variables collected, the outcome groups⁵⁰ differed on age at childhood assessment, IQ, social class, and marital status. The persisters were older at the childhood assessment, had a lower IQ, and were more likely to come from a lower social class, single parent-household compared to both desister groups. In a regression model,⁵¹ however, social class was the only significant demographic predictor of group outcome at follow-up and, thus, is the focus of the current discussion.

4.5.1.1 Social Class

The persisters were at increased odds of coming from a lower social class background compared to the desisters. However, within the two groups of desisters, social class did not predict outcome at follow-up. Thus, in this sample of boys with GID, social class was a predictor of gender identity outcome, but not of sexual orientation outcome per se. These results cannot be compared to previous follow-up studies as social class data were not published. There are a number of potential explanations for the relationship between social class and persistence of gender dysphoria such that social class may be a proxy for a number of factors, including familial stress, parental psychopathology, peer relations, attitudes towards effeminate gay men, and attitudes towards homosexuality, each of which is subsequently discussed.

⁵⁰ For analyses, only three of the four outcome groups (bisexual/homosexual persisters, bisexual/homosexual desisters, and heterosexual desisters) were compared. The heterosexual persister was excluded from the group analyses.

⁵¹ Predictor variables were age at childhood assessment, Full Scale IQ in childhood, social class, and marital status.

In the literature on adult homosexual and non-homosexual male-to-female transsexuals, there has been a long-standing observation that these individuals, on average, seem to grow up within families of low socioeconomic status (e.g., Hoenig, Kenna, & Youd, 1970; MacFarlane, 1984). The association between male-to-female transsexualism and sexwork (a correlate of socioeconomic status) has also been examined. A recent study of 573 self-identified adult transsexuals, for example, found that more than 50% had done some type of sexwork in the preceding 6 months (Nemoto, Bödeker, & Iwamoto, 2011). From these data, it is unclear whether low socioeconomic status was implicated in the etiology and development of transsexualism or whether it was secondary to possible social struggles and economic discrimination experienced by these individuals.

4.5.1.1.1 Familial Stress and Parental Psychopathology

Socioeconomic status (SES) or social class has a long-standing history in the child development literature as a risk factor for negative outcomes, with numerous studies demonstrating the association between poverty, for example, and increased risk for mental health problems in children (for a summary, see Jenkins, 2008). In the child development literature, social class has been conceptualized as a proxy or marker for access to resources and experiences that may be related to or associated with socioeconomic status (Bradley & Corwyn, 2002). For example, numerous studies have shown that low SES families experience, on average, significantly more stress compared to high SES families due to more destabilizing events, such as family dissolution and moves (e.g., Gad & Johnson, 1980).

Though speculative, it may be that low social class is a risk factor for persistent gender dysphoria due to the associated stress in these families. Parents who are experiencing significant stressors may be overwhelmed by these difficulties, feel depleted themselves, and,

thus, are unable to work on interventions aimed at resolving their child's gender identity issues (Zucker et al., 2012b). One can imagine that, if a family is burdened with economic hardship, there may be less financial resources to dedicate to addressing the child's gender identity issues. A consistent finding in psychiatric research has been the negative relationship between SES and mental disorder—the lower the SES of an individual, the higher is his or her risk for developing a mental disorder (e.g., Hollingshead & Redlich, 1958; Hudson, 1988, 2005). It may be that the parents of persisters were also struggling with significant psychopathology that interfered with their parenting role and this contributed to the perpetuation of their child's gender dysphoria. Data on parental psychopathology at the time of the childhood assessment were not analyzed as they were not the focus of the present study. Therefore, it remains unknown whether parents of persisters had more psychopathology compared to parents of the desisters. Zucker and Bradley (1995) reported that mothers of boys with GID were more impaired in their emotional functioning compared to mothers of normal control boys but were generally as impaired as mothers of clinical control boys.

4.5.1.1.2 Quality of Peer Relationships

Social class may also be operating on the quality of peer relations in the study participants. Peer relations are an important aspect of children's well-being in general (for a review, see Parker, Rubin, Price, & DeRosier, 1995) and, more specifically, relations with same-sex peers play an important role in children's gender identity development and consolidation (Maccoby, 1998). Thus, for children with GID, developing and expanding the breadth of same-sex peer relations with temperamentally compatible peers has been encouraged (e.g., Meyer-Bahlburg, 2002; Zucker et al., 2012b). Studies have shown that

children with GID have more peer relationship difficulties than their siblings and non-GID peers (e.g., Cohen-Kettenis et al., 2003; Zucker, Bradley, & Sanikhani, 1997). There is some evidence that children from low SES families may be more isolated from peers and experience less peer companionship overall compared to their high SES counterparts (Patterson, Vaden, Griesler, & Kupersmidt, 1991). It is possible that boys with GID who were also from a low SES may have had even fewer opportunities for using their peers for gender identity consolidation and, therefore, were at an increased risk for persistence of cross-gender identification compared to boys with GID from a higher social class background. In the present, sample, however, there was no significant difference between the outcome groups on the quality of their childhood peer relations, measured using two items from the Child Behavior Checklist. It is possible that our crude measure of childhood peer relations was not sufficient to capture differences between the groups on quality of their relationships, if differences did exist.

4.5.1.1.3 Attitudes towards Homosexuality

The stereotypical gay man in Western culture is feminine in a number of respects, including his mannerisms, interests, and occupation; however, there is variation in the extent of femininity seen in homosexual men (Bailey & Pillard, 1991; Rieger, Linsenmeier, Gygax, Garcia, & Bailey, 2010). An inverse relationship between social class and effeminacy in adult gay men has been reported, such that more stereotypical/effeminate behaviors are seen in gay men from a lower social class background compared to gay men from a higher social class (e.g., Farrell & Morrione, 1974). Given that a large proportion of gay men engaged in cross-gendered behaviors in childhood, a process of defeminization (Whitam, 1977) occurred in some gay men between childhood and adulthood while, in others, cross-gender behaviors

persisted. Harry (1985b) speculated that defeminization (i.e., discontinuation in cross-gender behaviors) may be related to social class such that it is more likely to occur among gay males from middle-class backgrounds than among males from working-class families, and found support for this hypothesis in a retrospective study of 686 male homosexuals. There was greater continuation of cross-gender behaviors among adult gay men raised in blue-collar households than those raised in middle-class/white-color households.

In the present study, the least amount of defeminization (i.e., persistence of cross-gender behaviors) did occur in boys from a lower social class while the most defeminization (i.e., desistence) occurred in boys from a higher social class. The relationship between social class and persistent gender dysphoria may be related to attitudes of gay men towards effeminacy in other gay men. Gay men, particularly those who view themselves as masculine, prefer men who describe themselves as masculine rather than feminine (Bailey, Kim, Hills, & Linsenmeier, 1997; Taywadietp, 2001). It is possible that males with persistent cross-gender behaviors who may or may not have yet desisted in their gender dysphoria would be experienced by homosexual men as effeminate and may, therefore, be rejected as sexual partners. Consistent rejection may predispose some of these individuals to consider transitioning to the female gender role as an alternative to living as a homosexual man. This hypothesized process may not occur in the lives of gay men who do not have a childhood history of gender dysphoria. However, in effeminate men with a homosexual sexual orientation and a history of gender dysphoria, it may increase the likelihood of a transsexual outcome. Future studies would need to systematically examine whether boys with persistent GID first attempt to live as homosexual men before transitioning to the female gender role and whether romantic rejection was experienced in the former. Consciously or

unconsciously, there may be a weighing of pros and cons in the minds of adolescent boys with GID who continue to be effeminate regarding their likelihood of being accepted or passing as a gay male or as (trans) female. Thus, it is possible that effeminate gay men with a history of gender dysphoria who experience rejection from gay men may decide that they may be more likely to be accepted as a (trans) female and may, therefore, pursue transitioning rather than live as a gay male. It is understandable that such experience may result in significant socioemotional difficulties, which may further predispose these individuals to persistent GID.

With one exception, the persisters in the study were bisexual/homosexual in sexual orientation. The relationship between social class and persistence of gender dysphoria may be related to attitudes about homosexuality. Three decades ago, Hellman, Green, Gray, and Williams (1981) retrospectively explored a number of factors that were hypothesized to influence the development of transsexualism and sexual orientation, including childhood femininity, childhood religiosity (specifically in Catholics), and homophobia, among homosexual males, heterosexual males, and male-to-female transsexuals. Hellman et al.'s (1981) interest in exploring the relationship between religiosity and Catholicism stemmed from statements of some transsexuals that homosexuality is immoral and, therefore, transsexualism may resolve the conflict between same-sex sexual attraction and religious beliefs that do not support same-sex attractions. Hellman et al. did not find support for the view that transsexualism was simply motivated out of conflict between religious beliefs and sexual orientation. Rather, homophobia among transsexuals seemed to have stemmed from the need to maintain established social values (i.e., heterosexuality is the appropriate behavior). It was reassuring that all groups scored low on an index of homophobia; however,

there were significant differences between the groups: the heterosexuals were the most homophobic and the homosexual men were the least homophobic. Not surprisingly, childhood femininity had the greatest influence on later transsexualism. However, when the level of femininity was not extreme, homophobia was significantly associated with a transsexual outcome. Hellman et al. speculated that childhood femininity in males and homophobia may interact to result in transsexualism in adulthood.

There is support for the idea that individuals who hold less favorable views of homosexuality may be less educated and belong to a lower social class compared to individuals who hold a more favorable view (e.g., Glenn & Weaver, 1979; Hill, 2002; Irwin & Thompson, 1977; Jensen, Gambles, & Olsen, 1988; Lemelle & Battle, 2004; Nyberg & Alston, 1976). There are a number of possible mechanisms through which social class may be related to attitudes about homosexuality. Higher education and, by extension, higher social class may foster more favorable attitudes towards homosexuality due to exposure to greater diversity (e.g., in people, ideas, philosophies) in higher education institutions (Herek & Capitanio, 1996; Herek & Glunt, 1993). Increased acceptance and approval of homosexuality may also reflect a larger set of changes in attitudes that takes place during higher education (Lottes & Kuriloff, 1994).

In the present study, the parents of persisters may have held less favorable views of homosexuality compared to the desisters. As a result, the persisters may have experienced more disapproval of homosexuality during development and were, therefore, more predisposed to a transsexual⁵² outcome compared to boys with GID who grew up in an environment that was accepting of homosexuality. This is, of course, speculative as parental

⁵² In the context of strong negative attitudes towards homosexuality, some might view a transsexual outcome as more favorable than a homosexual one because, in living as a woman, these individuals would typically self-label as heterosexual rather than as homosexual to reflect their female gender identity.

attitudes towards homosexuality were not measured in the study sample. None of the follow-up studies to date on boys with gender dysphoria have specifically examined attitudes towards homosexuality as a predictor of outcome. Given that negative attitudes towards homosexuality may also vary according to cultural background, it would be important to examine whether ethnicity, independent of social class, is predictive of gender identity outcome. In the present study, there was no significant difference in ethnicity between the persisters and desisters; however, this is not surprising given that the sample was predominantly of Caucasian background. As such, there may not have been sufficient variability in ethnicity to detect a difference if one does actually exist.

4.5.2 Childhood Sex-Typed Behavior as a Predictor of Gender Identity Outcome

Given Wallien and Cohen-Kettenis' (2008) finding that the persisters in their study were more extreme in their childhood cross-gender behaviors than were the desisters, it was not surprising that, in the present study, childhood sex-typed behavior was predictive of group outcome at follow-up. Of the nine measures of sex-typed behavior used in the present study, the groups differed on four child (self) report measures (three of which were dimensional) and one dimensional parent report measure, with the persisters having more extreme scores (i.e., more childhood cross-gender behavior) than both desister groups. Similarly, in Wallien and Cohen-Kettenis' study, the persisters had more extreme scores on two dimensional measures of cross-gender behavior and gender dysphoria,⁵³ both of which were used in the present study and on both the persisters were more extreme than were the desisters.

⁵³ The measures were the Gender Identity Questionnaire for Children and the Gender Identity Interview, both of which were developed in the Toronto gender identity clinic.

In a regression model,⁵⁴ both social class and childhood sex-typed behavior were predictors of gender identity outcome. Childhood sex-typed behavior was a predictor of gender identity above and beyond social class. The persisters were at substantially increased odds of having more extreme cross-gender behavior in childhood compared to the bisexual/homosexual desisters. These findings suggest that the severity of childhood cross-gender behavior has an impact on the developmental trajectory of boys with GID: Boys with more extreme cross-gender identity and behavior are more likely to show persistence of their gender dysphoria into adolescence/adulthood while those with less extreme cross-gender identification are more likely to overcome their gender dysphoria by the time they reach adolescence/adulthood, if not before.

In the present study, the persisters were no more likely than the desisters to have met the complete categorical DSM criteria for GID in childhood. It is possible that the diagnostic criteria for GID, in its current form, are not sharp enough to distinguish children who are more likely to show persistence of the disorder from those who are not (Zucker & Cohen-Kettenis, 2008).

4.5.3 Behavior Problems in Childhood as a Predictor of Gender Identity Outcome

Using the CBCL as a measure of behavior problems in childhood, there was no significant difference between the outcome groups: the persisters did not differ from the desisters on internalizing and externalizing problems in childhood. There was also no significant difference between the three outcome groups on the percentage of each group that fell within the clinical range on internalizing, externalizing, and total problems. Thus, childhood behavior problems did not appear to impact the developmental trajectory of gender

⁵⁴ Predictor variables were age at childhood assessment, Full Scale IQ in childhood, social class, and composite z-score of childhood sex-typed behavior.

dysphoria. This finding cannot be compared to previous follow-up studies of boys with GID. In Green's (1987) study, it was reported that the feminine group had few behavioral problems other than gender identity issues; however, Green did not systematically assess behavioral problems at the time of the childhood assessment. Wallien and Cohen-Kettenis (2008) did not provide data on associated behavior problems in their follow-up sample.

In recent years, a new line of research has suggested that some children with GID may have comorbid Pervasive Developmental Disorder (PDD) (e.g., de Vries et al., 2010). One explanation for a possible linkage between these two disorders is the intense focus on specific activities (e.g., Klin et al., 2007). This has led to some discussions about the relationship between PDD and GID and whether the presence of PDD would influence the trajectory of gender dysphoria. It is not clear if children with GID who also have PDD or traits of PDD will be more likely to persist in gender dysphoria compared to children with GID who do not have PDD or traits of PDD. It is plausible that the presence of a PDD may increase the likelihood of persistent gender dysphoria if the fixation on cross-gender interests in these children is more intense compared to children with GID without a PDD. On the other hand, for some children with PDD, the nature of the intense interest does change over time and, therefore, comorbid PDD may not place children with GID at a greater risk for persistent gender dysphoria. This is an empirical question that will require further exploration.⁵⁵

In addition to social class and severity of cross-gender behavior in childhood as predictors of persistent gender dysphoria, there may well be additional factors that contributed to persistence and desistence of GID from childhood into adolescence, though it

⁵⁵ In the present follow-up sample, the presence of a PDD was not assessed at follow-up as the semi-structured diagnostic interviews did not include a module to assess for PDD.

would be a matter of speculation as they were not measured in the study. It is possible that psychotherapy that aims to reduce gender dysphoria can alter the course of GID and make it less likely that the child will persist (e.g., Green, 1974; Cohen-Kettenis & Pfäfflin, 2003; Zucker, 2006c). Perhaps parents' and clinicians' attempts to modify children's cross-gender behaviors result in a reduction of the behaviors, thereby enabling children to socialize as members of their birth sex and preventing the need for a sex change (Green, 2008). However, treatment studies with long-term follow-up are required to support this explanation. None of the follow-up studies to date, including this study, have systematically examined treatment received between the childhood assessment and follow-up.

Persistence of gender dysphoria may reflect a continuation of the psychosocial risk factors that contributed to its genesis in the first place. As one example, Zucker et al. (2012b) suggested that parental response to cross-gender behavior as it emerges in development is an important parameter in the clinical case formulation of gender-referred children. In this model, parental neutrality and parental encouragement of cross-gender behavior are both viewed as perpetuating factors in the child's cross-gender identification. There is some support for this idea. In Green's (1987) follow-up study, the degree to which mothers of the feminine boys were rated as supportive of the boy's early cross-gender behavior (i.e., did not make an attempt to interrupt the cross-gender behaviors) rather than masculine behavior was significantly correlated with a rating of childhood "femininity" that was derived from the combination of six variables of cross-gender behavior (e.g., doll play, cross-dressing). Clinical impression in the assessment of adolescents with GID (where the rate of persistent gender dysphoria seems to be much higher than seen in children) is that their parents display more tolerance towards cross-gender behavior than do parents who seek consultation when

their children are younger (Bradley & Zucker, 1997). One can reasonably hypothesize, then, that continued parental neutrality or encouragement of cross-gender behaviors in children with GID after the disorder develops may increase the chances of persistent gender dysphoria in adolescence and adulthood.

4.6 Variation in Persistence Rates across Follow-up Studies of Boys with GID

As previously noted, the rates of persistent gender dysphoria obtained in the present study and by Green (1987) and Wallien and Cohen-Kettenis (2008) were significantly different. The persistence rate obtained in the present study was significantly lower than that obtained by Wallien and Cohen-Kettenis in their sample of boys with GID. Similarly, when one compares the persistence rate of the females in Wallien and Cohen-Kettenis' study to that obtained by Drummond et al. (2008) in their follow-up study of girls with GID, there was significant variability across the two studies, with the former reporting a significantly higher persistence rate than the latter.⁵⁶ When the results from the present study were combined with the persistence rate obtained by Drummond et al. (2008) and then subsequently compared to the persistence rate obtained by Wallien and Cohen-Kettenis for boys and girls combined, there was also a significant difference. This raises the issue of cross-clinic, cross-national factors that may be contributing to variability in persistence rates, including sample composition, socio-cultural influences, differences between referred and non-referred families, and treatment experience, each of which is discussed below.

⁵⁶ Wallien and Cohen-Kettenis (2008) reported that 9 of the 14 girls who were successfully traced at follow-up were gender dysphoric and the remaining 5 girls were desisters, which yielded a persistence rate of 64.2%. However, an additional 4 girls could not be traced at follow-up and were assumed by Wallien and Cohen-Kettenis to be desisters. When these participants were included in the calculation of a more liberal persistence rate, persistence dropped to 50%. Regardless of whether one uses the liberal or more conservative persistence rate, the rates obtained by Wallien and Cohen-Kettenis were substantially higher than the 12% persistence rate obtained by Drummond et al. (2008).

4.6.1 Sample Differences

Sample differences in severity of cross-gender behavior, age at childhood assessment, social class, and treatment may have contributed to the variability across studies in the rate of persistent gender dysphoria.

Zucker and Seto (2008) speculated that some of the previously observed variability in persistence rates may be attributable to sample differences as Wallien and Cohen-Kettenis (2008) reported on a clinically referred sample while Green (1987) reported on a non-clinical (advertised) sample that may have contained less extreme participants with respect to severity of cross-gender identification. Thus, a referral bias may be at play and account for the variability in persistence rates obtained by Green and Wallien and Cohen-Kettenis. A direct comparison could not be made between the boys in the present study and those in Wallien and Cohen-Kettenis' study with respect to scores on specific measures of sex-typed behaviors.⁵⁷ However, comparisons of the Amsterdam and Toronto clinics on severity in clinical presentation of the children assessed at each clinic have provided some evidence to suggest that, on average, children referred to the Amsterdam gender clinic may be more extreme in their cross-gender identification compared to children referred to the Toronto gender clinic.

Cross-clinic (i.e., Amsterdam vs. Toronto) severity in clinical presentation could be measured in two ways. One approach involves comparing clinic-referred children from Toronto and Amsterdam on validated dimensional measures of sex-typed behavior. Cross-national, cross-clinic studies comparing boys with GID seen at our clinic in Toronto to boys

⁵⁷ Wallien and Cohen-Kettenis (2008) did not publish overall sample means and standard deviation on these measures, therefore precluding direct comparison to the boys in the present study.

seen at the Amsterdam gender clinic⁵⁸ found that boys seen in Amsterdam were, on average, more extreme in their cross-gender behaviors. The finding was consistent across self-report on the Gender Identity Interview (Wallien et al., 2009) and parent-report on the Gender Identity Questionnaire for Children (Cohen-Kettenis et al., 2006).

A second approach to measuring severity involves a comparison of the percentage of children from each clinic who meet full diagnostic criteria for GID. Cohen-Kettenis et al. (2003) conducted a cross-clinic comparison of children seen in Amsterdam and Toronto and found that a greater percentage of children seen at the Amsterdam clinic met full criteria for the DSM diagnosis compared to children seen at the gender clinic in Toronto. In fact, there was a 227% increase in the odds of meeting the complete DSM criteria for GID in the Amsterdam clinic compared to the Toronto clinic. This finding added support to the possibility that boys seen in the Amsterdam clinic were, on average, more extreme than boys seen in the Toronto clinic. It is possible, then, that (by extension) the boys in Wallien and Cohen-Kettenis' follow-up study were more extreme in their childhood cross-gender behaviors compared to the boys in the present study. However, there was no significant difference between the present follow-up study and follow-up study by Wallien and Cohen-Kettenis (2008) in the percentage of boys in the respective samples that were given the full DSM diagnosis of GID in childhood. Thus, while the results of cross-clinic comparisons of the children seen at the Toronto and Amsterdam clinics suggest that children assessed in Amsterdam may be more extreme than children assessed in Toronto, it remains unclear whether the boys in the present study were, in fact, less extreme compared to the boys in Wallien and Cohen-Kettenis' follow-up study.

⁵⁸ To clarify, Wallien and Cohen-Kettenis' research was conducted at the specialized gender identity clinic in Amsterdam, which I sometimes refer to as the Dutch or Amsterdam clinic.

The boys in Wallien and Cohen-Kettenis' study were, on average, older at the time of the childhood assessment compared to the boys in the present study. This fits with comparative data on age at referral for gender identity concerns, which show that children in Toronto are generally referred at a younger age compared to children in Amsterdam (Cohen-Kettenis et al., 2003). It is possible that sample differences in age at assessment and severity of cross-gender behavior in childhood contributed to the variation in the rates of persistent gender dysphoria in the two studies. Discussed later, differences in treatment approaches across the clinics might have also contributed to variation in persistence rates.

The participants in the present study may have also differed from those in Green's and Wallien and Cohen-Kettenis' studies along dimensions of other factors that may influence the developmental trajectory of gender dysphoria. In the present study, for example, social class was a predictor of gender identity outcome with persisters more likely to originate in families from lower social class background compared to desisters. One can speculate that perhaps the participants in the present study differed from those in Green's and Wallien and Cohen-Kettenis' study in social class background, which could have contributed to the variability in persistence rates across the three studies. This is speculative, however, as data on social class of their participants were not available in the publications by Green (1987) and Wallien and Cohen-Kettenis (2008).

Mentioned earlier, psychotherapy may alter the course of GID; however, this variable was not measured in the present study or by Wallien and Cohen-Kettenis, which makes it impossible to make comparisons. A possibility is that, not only could there have been sample differences in whether participants received therapy between the childhood assessment and follow-up, but there may have been differences in the treatment approaches to childhood

gender dysphoria. In the Dutch approach to treatment of children with GID, therapy is not directed at the gender dysphoria itself and instead focuses on concomitant emotional or behavioral problems in the child and dysfunctional family dynamics (de Vries & Cohen-Kettenis, 2012). At the gender clinic in Toronto, the specific goals of therapy are guided by the clinical formulation. In some cases, the focus of therapy is solely on resolving the child's gender dysphoria and in other cases therapy may focus on gender dysphoria in addition to other emotional/behavioral problems identified by the parents. In instances where parents are unclear of how to proceed vis-à-vis their child's cross-gender identification, resolving the child's gender dysphoria may not be the focus of therapy (Zucker et al., 2012b). It is an important empirical question whether these variations in treatment approaches across the Toronto and Dutch clinics have contributed to the variation seen in the percentage of children from each clinic who persist in their gender dysphoria. It is possible that a therapeutic approach that focuses on resolving a child's gender dysphoria may result in a greater likelihood of desistence compared to an approach does not directly address the gender dysphoria. To address this issue, systematic treatment studies with long-term follow-up would be required.

Green (2008) suggested that a cohort effect may also explain why the more recent study by Wallien and Cohen-Kettenis (2008) found a higher persistence rate than his follow-up study conducted over two decades ago. Green (2008) hypothesized that, over the years, society's increasing tolerance for cross-gender behavior in children might have raised the threshold for clinical referral. As such, children assessed three decades ago may have been less extreme in their cross-gender behavior because the threshold for referral was lower at that time. Thus, children referred more recently are more extreme in their cross-gender

behavior and, therefore, more likely to show persistence of gender dysphoria. In the present study, childhood assessment data were collected over a 30-year period. The severity of sex-typed behavior did not vary as a function of year of assessment. Contrary to Green's hypothesis, the boys seen 30 years ago were, on average, no less severe in their childhood cross-gender behaviors than boys seen in past 10 years.

4.6.2 Sociocultural Influences

There is some merit to Green's stipulation that societal tolerance for cross-gender behavior may impact the threshold for becoming concerned about children's cross-gender behavior and a subsequent referral to a gender clinic. In a cross-clinic comparison on the Gender Identity Interview, it was observed that children from the Toronto clinic were more guarded than their Dutch counterparts in acknowledging cross-gender feelings (Wallien et al., 2009). Moreover, older children in the Toronto sample were less likely to report cross-gender feelings whereas this was not seen in the Dutch sample. Wallien et al. (2009) hypothesized that perhaps the Dutch children were less inhibited and more candid about sharing cross-gender feelings because their culture, on average, is more tolerant of cross-gender behaviors compared to Toronto culture. At the same time, Dutch children with GID experience similarly poor peer relations as children with GID seen in Toronto (Cohen-Kettenis et al., 2003; Wallien et al., 2009). A similar sociocultural hypothesis was offered to explain the older age of referral seen among Dutch children with GID compared to children seen in Toronto (Cohen-Kettenis et al., 2003). Perhaps the parents of Dutch children with GID were relatively less concerned about their children's early cross-gender behavior compared to their Toronto counterparts and, therefore, a greater period of time elapsed between onset of cross-gender behaviors and the clinical assessment.

Cross-cultural differences in attitudes towards children's cross-gender behavior may also play a role in the variability in persistence rates seen across the Dutch and Toronto clinic. As noted previously, some clinicians (e.g., Green, 1987; Zucker et al., 2012b) have suggested that parental tolerance of children's cross-gender behaviors may encourage/perpetuate the behaviors, which may increase the likelihood of persistence of the behaviors into adolescence. If Dutch parents are, on average, less concerned and more tolerant of their children's cross-gender behaviors compared to Toronto parents, this may have contributed to the higher persistence rate of gender dysphoria obtained by Wallien and Cohen-Kettenis (2008). Of course, cross-clinic data on parental attitudes towards cross-gender behavior would be needed to evaluate this hypothesis.

The issue of sociocultural influences regarding GID raises a question about the influence of society's attitudes about cross-gender behaviors on persistence and desistence rates. The *fa'afafine* is a clearly defined third gender in Samoa, a society in which there is considerable acceptance and support of boys who take on the social roles of females (Vasey & Bartlett, 2007). In a retrospective study, most *fa'afafine* recalled that they frequently engaged in cross-gender behaviors in childhood and some adopted a cross-gender identity, believing they were girls (Vasey & Bartlett, 2007). One can, therefore, conceptualize *fa'afafine* as biological males who show persistence of childhood cross-gender behavior into adulthood. An empirical question is raised about whether there would be a higher persistence rate of cross-gender behaviors and identification from childhood into adolescence and adulthood in Samoa, or societies in which gender is not a binary construct, compared to societies in which gender is conceptualized as a binary construct. Using the Samoan culture as an example, there have been no published data on whether boys who are identified as

fa'afafine in childhood grow up to later identify as males and, therefore, desist in their *fa'afafine* identity.

4.6.3 Referred vs. Non-Referred Children

It is also important to consider that parents who bring their children to a gender identity clinic may differ in attitude towards cross-gender behavior from parents who choose not to have their child seen by a professional. This raises a larger issue of how representative clinically referred children with cross-gender behavior are of all children with similar behaviors. For the most part, the prospective studies of boys with GID reported on samples of clinically referred children. The notable exception was Green's (1987) sample, which was recruited through advertisement. It is unclear if and how these children, and their families, differ from families who choose to not seek professional consultation. Perhaps parents of non-referred children are less concerned compared to parents who seek professional services for their child's cross-gendered behaviors. However, some parents of extremely cross-gendered children who do not seek an assessment/treatment may be ambivalent about how to address the issue or may be avoiding it all together. Given the obvious difficulty of conducting a study of parents who do not seek professional help, we simply do not know how treatment-seeking families differ from non-treatment seeking families and whether these differences can affect the development trajectory of the child's gender identity, and ultimately affect persistence/desistence of gender dysphoria. It is also possible that the assessment process itself, regardless of whether psychotherapy is subsequently received, alters the natural history of cross-gender identification in some referred children, thus reducing the risk for persistent GID.

4.6.4 Treatment Experience

There is another reason to speculate that the families seen at the clinic in Toronto may be different from families that do not seek professional help for their cross-gender identified child and also from families who seek help at other clinics. The clinic's philosophy around treatment of gender dysphoria in children has been publicized in mainstream local media (e.g., *Toronto Life* magazine, *The Agenda* with Steve Paiken). Parents of cross-gender identified children who believe that their child is inherently transgendered and who do not view their child's cross-gender identification as psychopathological may seek the support of clinicians who support transition rather than attend a clinic where the treatment philosophy does not include explicit support for gender transitioning in childhood. It is possible that the children referred to our clinic and, by extension, the participants in the study may represent a biased sample. One therefore wonders whether the persistent rate obtained is representative of the persistent rate within the overall population of children with GID.

4.7 Implications of High Desistence Rate

4.7.1 Theoretical Implications

In comparing the long-term outcome of children with GID obtained in prospective studies to retrospective studies of adolescents and adults with GID, a notable disjunction with regard to gender identity outcome is observed. While adolescent and adult males with GID, particularly those who are androphilic,⁵⁹ recall a pattern of childhood cross-gender behavior that is consistent with the phenomenology of GID, most children with GID do not continue to have GID in adulthood. How might this disjunction be understood? Children with GID have different developmental trajectories and this leads to diverse outcomes in adolescence and adulthood. Perhaps there is malleability or plasticity in gender identity differentiation early

⁵⁹ Sexually attracted to biological males.

on in development; however, it becomes more fixed as development progresses into adolescence and adulthood (Coates & Wolfe, 1997; Meyer-Bahlburg, 2002; Zucker, 2006a; Zucker & Bradley, 1995).

Clinical observation and empirical evidence support this idea—persistence of gender dysphoria, including the desire for sex change, is higher among patients assessed for the first time during adolescence and then followed up than among patients first assessed in childhood and then followed prospectively (Zucker & Bradley, 1995). In Cohen-Kettenis and van Goozen's (1997) follow-up study of Dutch adolescents with GID, the rate of persistent gender dysphoria was 66.6%. This is similar to the percentage of adolescents recommended for puberty blocking hormonal treatment at the Toronto clinic (Zucker et al., 2011). If we assume liberally that the adolescents recommended for puberty blockers would persist in their gender dysphoria, the persistence rates obtained by Cohen-Kettenis and van Goozen and Zucker et al. in their adolescent samples are substantially higher than that obtained in the follow-up studies of boys with GID first referred in childhood. That gender identity is relatively more malleable in childhood but becomes less plastic as development progresses may also explain why the persisters were significantly older at the time of the childhood assessment compared to the desisters.

Another explanation for the disjunction between rates of persistence of GID in children versus adolescents may pertain to the differences in the DSM criteria for these age groups (Drummond et al., 2008). The criteria for GID in children places relatively greater emphasis on surface behavior indicators of cross-gender identification, whereas the criteria in adolescence (and adulthood) relies more heavily on behaviors and feelings stemming from the conflict between subjective gender identity and somatic sex (i.e., anatomic dysphoria).

Thus, the childhood criteria for GID may also be capturing children that are at relatively low-risk for persistent GID while the diagnostic criteria for GID in adolescents and adults, with its emphasis on somatic indicators (e.g., in males, distress about facial hair, deepening of voice), may be capturing primarily the high-risk for transsexualism/persistence group.

4.7.2 Clinical Implications

That most boys did not continue to experience gender dysphoria in adolescence and adulthood and reported feeling happy and comfortable living as males raises the issue of “best practice” in clinical management of GID. At present, there are three therapeutic approaches for GID, each informed by distinct conceptual and philosophical assumptions regarding gender identity development: one actively attempts to work with the children and their parents to lessen the child’s gender dysphoria; in a second approach, there is no active attempt to lessen the child’s gender dysphoria or cross-gender behaviors; and a third, more recent, approach actively encourages gender transitioning in childhood and puberty blocking hormones as puberty approaches (if the gender dysphoria persists). The third approach has recently been featured on popular TV shows such as the *Oprah Winfrey Show*, *20/20*, and *Anderson Cooper*. Two important questions regarding therapeutics for children with GID are raised: (1) Should gender transition be encouraged in childhood given that most boys with GID will not continue to experience gender dysphoria later in life, and (2) Do the various treatment approaches for children with GID have different long-term gender identity outcomes?

4.7.2.1 Should Gender Transitioning be Encouraged in Childhood?

An early gender transitioning approach appears to stem from a theoretical standpoint that the persistence or desistence of gender dysphoria occurs in isolation and is not

influenced by biological, psychological, or social factors. To some extent, there also seems to be the assumption that gender identity is fixed at an early age and is not malleable. While this may be true for the vast majority of children, there are some children whose gender identity does change. The high desistence rate obtained in follow-up studies suggested that, for some children, gender identity is not fixed at an early age and is, indeed, malleable. Thus, one needs to consider if they want to encourage early transition and, hence, a pathway of complex medical treatment (cross-sex hormonal treatment, sex-reassignment surgery) without first trying to understand the nature of a child's gender identity and whether there is any room for helping the child develop a gender identity that is aligned with their biological sex.

Apart from case reports (e.g., Ehrensaft, 2011, 2012), there is little in the way of published data on the experience of children who transition in childhood. As there have been no follow-up studies of these children; at this time, one can only speculate about potential risks of this approach. There are reports that some children who engage in a social transition in childhood later on reverse their gender role transition and return to a gender role that is aligned with their biological sex (e.g., Edwards-Leeper & Spack, 2012; Menvielle, 2012). At the present time, however, it remains unknown what percentage of these children later reverse their transition. One has to consider the potential risk of harm to children who are encouraged to transition early but who later experience resolution of their gender dysphoria and want to reverse their transition.

In the qualitative study by Steensma et al. (2011) on 25 adolescents who had been diagnosed with GID in childhood, two girls who had lived as boys, and were treated as such but had not officially transitioned, during elementary school reported that they found it very

difficult to return to the female gender role once they realized that they no longer wanted to live in the opposite gender role (presumably because their gender dysphoria resolved). Fear of teasing and shame to admit they were “wrong” about wanting to transition prolonged these children’s distress, though they did eventually return to their female gender role in high school. One can imagine how difficult it would be for children who had socially transitioned in childhood and who were living for years as the opposite sex to make a change back, particularly if only their immediately family were aware of their biological sex (de Vries & Cohen-Kettenis, 2012). Some children could conceivably feel “stuck” in the opposite gender role even if their gender dysphoria desisted as they had committed themselves, parents, and others in their life in supporting their transitioning. Some children may not disclose that they no longer want to live as the opposite gender and may, therefore, maintain a transgendered presentation even if it conflicts with their felt gender identity. Thus, the decision to support an early transition raises the concern that a child may not feel free to switch back to a gender role aligned with his or her biological sex if he or she desires to do so in the future, a concern that is acknowledged by some clinicians who are supportive of early gender transitioning (e.g., Edwards-Leeper & Spack, 2012).

de Vries and Cohen-Kettenis (2012), in their description of the Dutch approach to treatment of children and adolescents with GID, provided an additional rationale for not recommending early transition. There is concern that children who transition very early (e.g., in preschool) may not realize that they are of the other natal sex and develop a sense of reality that is different from their physical reality that makes acceptance of the multiple treatments they will later need an unnecessarily difficult process.

At the same time, one also has to consider the possible advantages of an early transitioning approach. At the present time, we do not know whether the various treatment approaches will differentially affect the long-term psychiatric functioning and overall adjustment of these children. If, for example, persisters showed a better psychosocial adjustment and adaptation than children who desist (e.g., become homosexual or heterosexual without gender dysphoria), then one can question whether treatment efforts to maximize the chances of desistence (and prevent persistence) should be the optimal treatment goal (Zucker et al., 2012b). The argument can also be made that, for children who will turn out to be persisters, an early gender transitioning may be beneficial as there may be drawbacks to having to wait until puberty or adolescence to begin gender transitioning (Steensma & Cohen-Kettenis, 2011). However, the problem remains in the difficulty in distinguishing the persisters from the desisters at a young age. If it were possible to know with certainty whether a child with GID will persist or desist, then the clinical approach can be modified to best match the child's needs. In the absence of perfect science, combined with the high chances that gender dysphoria will desist and possible risk to those who transition in childhood but then want to reverse the transition, clinicians should be cautious in recommending gender transitioning in childhood. It is conceivable that the drawbacks of having to wait until early adolescence to begin transition may be less serious than having to make a social transition twice (Steensma & Cohen-Kettenis, 2011).

4.7.2.2 Effects of Treatment on Long-Term Gender Identity Outcome

A second important question is whether these various treatment approaches will result in different long-term gender identity outcomes for these children (Drescher & Byne, 2012). For example, will the rate of persistence be higher for children who are allowed to gender

transition at a young age compared to children for whom there is some attempt to lessen their gender dysphoria and cross-gender behaviors? In the clinical management of adolescents with gender dysphoria, one of the rationales for recommending puberty blocking hormonal treatment is that suspension of the patient's biological puberty will reduce their preoccupation with it and, therefore, afford the adolescent greater opportunity to explore his or her long-term gender identity options in psychotherapy in a less pressured manner (Edwards-Leeper & Spack, 2012; Zucker et al., 2011). In a review of current treatment approaches, Stein (2012) suggested the possibility that temporarily stopping puberty may have the effect of increasing persistence. Thus, instead of allowing adolescents more time to "wait-and-see" and evaluate their gender identity options, puberty blocking treatment may unintentionally push adolescents towards cross-sex hormonal treatment and sex-reassignment surgery.

Along the same lines, one can hypothesize that allowing children to socially transition in childhood may have the effect of increasing the chances of persistence into adolescence and adulthood. Without empirical comparative data on treatment approaches, one can only speculate on the effects of treatment on gender identity outcomes, if there are effects. At the follow-up assessment, participants in the present study were asked if they previously received treatment; however, a qualitative assessment of the interview data would be required to draw any substantial conclusions, which was beyond the scope of the present study. At the same time, it can be commented that some of the persisters in the study received treatment efforts aimed at helping them to resolve their gender dysphoria while in other cases much in the way of intervention was not attempted. The same can be said for the desisters.

4.7.3 Process of GID Desistence and Persistence Overtime

The present study advances our understanding of the long-term trajectories of boys with GID and the characteristics of the subgroup of the boys who persisted in their gender dysphoria into adolescence and adulthood. Gender identity appears to be relatively malleable in childhood, but becomes less plastic as development progresses. However, the factors that underlie this malleability are far from understood. We still do not know why most boys with GID “lose it” by adolescence or adulthood. We also do not understand the process of how desistence occurs and the possible interaction that occurs between biological and psychosocial variables to give rise to the observed trajectories in these children.

There have been no quantitative follow-up studies that have systematically examined the developmental process through which GID desists (e.g., how and at what age). Some authors suggest that desistence typically occurs sometime around puberty or early adolescence (de Vries & Cohen-Kettenis, 2008; Wallien & Cohen-Kettenis, 2008). However, one should be skeptical in viewing puberty as *the* transformative period in the lives of children with GID with regard to their gender identity. Some gender-referred children show changes in their gender identity before puberty and, in fact, desist in their dysphoria during childhood (for case examples, see Zucker, 2006c; Zucker & Bradley, 1995). In Steensma et al.’s (2011) qualitative study, persisters and desisters reported that the period from age 10 to 13 years of age was significant in the trajectory of their gender identity development. Whether gender dysphoria intensified or lessened appeared to have been influenced by psychosocial influences (e.g., peer relations), psychological factors (e.g., anticipation about puberty), and emerging sexual attraction. It is unclear how these factors interacted with other factors that have been hypothesized to influence the trajectory of GID, including therapy,

family dynamics, and biological factors (e.g., temperament, a genetic predisposition to cross-gender behaviors).

It was beyond the scope of this study to systematically evaluate when and how the desisters stopped experiencing feelings of gender dysphoria. This type of question would be best evaluated using a prospective study that included multiple follow-up assessments around critical time points in children's development (e.g., school entry, onset of somatic puberty). Notwithstanding, participants who reported desistence of gender dysphoria were asked about their thoughts on when and how it occurred. These data were not evaluated or coded in any systemic way and, therefore, can only be commented on qualitatively. Some participants stated that the gender dysphoria simply went away but could not offer any hypotheses on how nor could they remember when. Some desisters recalled feeling comfortable about their biological status as males long before puberty. Further, some desisters who were assessed early in childhood had no memory of earlier gender dysphoria and, in fact, were surprised to hear that they had, at one point, expressed a desire to be female. Clearly, desistence occurred during childhood for these males.

4.8 Variability in the Group of Persisters

On the Gender Identity Questionnaire for Adolescents and Adults, a dimensional measure of gender dysphoria, all but two persisters met criteria for caseness (of gender dysphoria), one of whom was the lone heterosexual persister, and the other was the youngest persister in the study. At the same time, based on interview data, there was notable variability in degree of gender transitioning within this subgroup. At the least extreme end of the spectrum were the participants who reported feelings of gender dysphoria but, at the same time, were not presenting socially as women, using a female name, or receiving any type of

hormonal treatment (i.e., hormones to suppress masculinization, cross-sex hormones)—there were at least four such participants. At the most extreme end of the spectrum were the participants who were presenting socially as women (e.g., wearing female clothing and make-up), had legally changed their name, and were taking cross-sex hormones to feminize their bodies. Although none of the persisters had undergone any type of surgery at the time of follow-up, some expressed interest in pursuing this type of medical treatment.

Additional details regarding these gender change parameters would be needed from Wallien and Cohen-Kettenis (2008) regarding the persisting males in their sample to make comparisons.⁶⁰ However, it appears that there was relatively less variability in their groups as all of the persisters had applied for sex reassignment by the age of 16 years. Therefore, as a group, the male persisters in Wallien and Cohen-Kettenis' study seemed more extreme in their gender dysphoria (at follow-up) compared to persisters in this study. There was no significant difference in the mean age at follow-up between the two groups; however, there was less variability in the age at follow-up in Wallien and Cohen-Kettenis' sample (16-18 years) compared to the present sample (13-39 years). Additional follow-up assessments with the younger persisters in the present study, particularly with those who were experiencing gender dysphoria but had not initiated any form of gender transition, would clarify how many of these males continue to persist in their gender dysphoria and how many, if any, desist. Therefore, to better understand the long-term outcome of boys with GID, longer follow-up periods that extend into adulthood are necessary.

⁶⁰ In other follow-up studies of boys with GID, the number of persisters was small; therefore, variability would not be expected. The lone persister in Green's (1987) study desired sex-reassignment surgery. In the six follow-up studies summarized by Zucker and Bradley (1995), 2 of the 5 individuals described as having a "transsexual" outcome were taking cross-sex hormones and 1 had completed sex-reassignment surgery. In the remaining two cases, details on degree of transitioning were not provided.

The variability in cross-gender identification among the persisters is not completely surprising. Individuals who present to gender identity clinics in adolescence are a heterogeneous group (e.g., Cohen-Kettenis & Pfäfflin, 2003, 2010; Meyer et al., 2001; Zucker et al., 2011). While most gender dysphoric adolescents who present to specialized gender identity clinics are seeking some form of biologic treatment (e.g., cross-sex hormones, sex-reassignment surgery), some gender dysphoric individuals do not request medical intervention and do not necessarily want to live in the opposite gender role (Cohen-Kettenis & Pfäfflin, 2003; Zucker et al., 2011). It is possible that the latter population may be representing individuals who are subthreshold for the DSM diagnosis of GID and, therefore, experience less gender dysphoria compared to individuals who desire sex reassignment surgery. Indeed, Cohen-Kettenis and Pfäfflin (2003) described the subthreshold adolescents seen in their clinic as a “heterogeneous group.” Some enter the clinic with a strong desire for sex-reassignment but later change their minds while others enter the clinic without a wish for sex reassignment but are confused about their gender identity and desire professional consultation. Some of these adolescents are ego-dystonic homosexual and, in others, the gender dysphoria is secondary to other psychopathology, such as a Pervasive Developmental Disorder. Interest in measuring gender dysphoria as a dimensional construct has been driven, in part, by the observed heterogeneity in adolescents and adults with GID (e.g., Deogracias et al., 2007; Singh et al., 2010).

4.9 Predictors of Sexual Orientation Outcome

As discussed above, the results of the present study were consistent with previous follow-up studies of effeminate boys and boys with GID that have shown that childhood cross-gender behavior and identification is associated with a high rate of bisexual/

homosexual outcome. These data also converge nicely with retrospective studies of homosexual men (Bailey & Zucker, 1995) and cross-cultural studies of men attracted to men (e.g., Bartlett & Vasey, 2006). At the same time, 33.3% of the participants reported a heterosexual outcome at follow-up. In follow-up studies by Green (1987) and Wallien and Cohen-Kettenis (2008), 25% and 19% of the participants, respectively, reported a heterosexual sexual orientation at follow-up. The relationship between age and “coming out” may, in part, account for this finding, as discussed earlier. However, that some males with GID develop a heterosexual outcome is not fully understood.

Wallien and Cohen-Kettenis (2008) hypothesized that perhaps degree of cross-gender identification in childhood may affect sexual orientation outcome, but they did not find support for this in their sample—differences in severity of childhood cross-gender behavior between the heterosexual and homosexual participants was obtained only for the persisters and not the desisters. In Green’s (1987) study, the results were mixed. On one hand, there was a significant correlation between childhood peer interest and doll play and adult sexual orientation in fantasy. However, within the group of feminine boys, there was no significant correlation between an overall femininity score and later sexual orientation.

In the present study, there were significant group differences between the bisexual/homosexual persisters, bisexual/homosexual desisters, and heterosexual desisters on five of nine measures of childhood sex-typed behaviors. In each instance, the persisters were more extreme in cross-gender identity/behaviors than were the two desister groups. In addition, there was some support for the idea that perhaps severity of cross-gender behavior may not only predict gender identity outcome, as discussed earlier, but also sexual orientation outcome. On one of the nine measures of childhood sex-typed behavior (Free Play), the

bisexual/homosexual desisters were less extreme than the bisexual/homosexual persisters but more extreme than the heterosexual desisters. Though speculative, it is possible that the bisexual/homosexual desisters and heterosexual desisters did not show more group differences because some of the males who identified as heterosexual may later identify as bisexual/homosexual. Of course, subsequent follow-up of the heterosexual group would be needed to evaluate this hypothesis. In a regression model,⁶¹ a composite measure of childhood cross-gender behavior was the only predictor of outcome when the heterosexual desisters were compared to the bisexual/homosexual desisters. The bisexual/homosexual participants were at increased odds of having more extreme childhood cross-gender behaviors compared to the heterosexual desisters.

These results suggest that there is also an association between severity of childhood cross-gender behavior and sexual orientation outcome. Within the desistence group, the boys who were more cross-gender identified developed a bisexual/homosexual sexual orientation and the boys who were less extreme in their cross-gender identification developed a heterosexual sexual orientation. As discussed earlier, there was also a “dosage effect” in the relationship between childhood cross-gender behavior and gender identity outcome. However, the dosage effect appears to be stronger in separating the persisting from the desisting cases (the bisexual/homosexual persisters had a 274% increase in odds of having more extreme childhood cross-gender behavior compared to the bisexual/homosexual desisters) than in separating the bisexual/homosexual desisters from the heterosexual desisters (the bisexual/homosexual desisters had a 48% increase in odds of having more extreme childhood cross-gender behavior compared to the heterosexual desisters).

⁶¹ Predictor variables were age at childhood assessment, Full Scale IQ in childhood, social class, and a composite measure of childhood sex-typed behavior.

The relationship between variation in degree of childhood cross-gender behavior and later sexual orientation has been demonstrated in epidemiological samples drawn from non-clinical populations. In a 24-year follow-up of 406 boys taken from a population based study and who were, therefore, unselected for their gender identity, those who were considered gender variant on a parent-report measure of behavior problems were more likely to develop a minority sexual orientation outcome compared to those who were classified as non-gender-variant (Steensma et al., 2012). Depending on whether sexual orientation was classified according to fantasy or behavior, the prevalence of bisexuality/homosexuality within the gender variant group was 8.7-9.5 times higher than that in the non-gender-variant group.

4.10 Behavioral Problems and Psychiatric Functioning at Follow-up

4.10.1 Behavior Problems at Follow-up

There were significant correlations between maternal ratings of behavior problems in childhood and at follow-up on three indices of disturbance: internalizing, externalizing, and total problems. Thus, the participants who were rated by their mothers as more extreme in behavior problems in childhood were also rated as more extreme in behavior problems at follow-up. However, maternal ratings in childhood did not correlate significantly with self-report at follow-up. At follow-up, however, there were significant correlations between participants' self-report and maternal report on internalizing, externalizing, and total problems. Thus, participants and their parents were generally in agreement on the extent of participants' behavioral problems at follow-up.

Behavior problems as a function of gender identity and sexual orientation identity at follow-up were examined in two ways. The three (primary) outcome groups (bisexual/homosexual persisters, bisexual/homosexual desisters, and heterosexual desisters) were

compared on three indices of disturbance (internalizing *T* score, externalizing *T* score, and total *T* score) using self-report on the Youth Self Report (YSR) or Adult Self Report (ASR) and maternal report on the Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL). The outcome groups were also compared on the percentage in each group whose *T* score fell within the clinical range on these three indices of disturbance. Based on maternal report, there were no significant differences between the three groups on internalizing, externalizing, and total problem or on the percentage of each group who fell within the clinical range. Significant group differences emerged, however, when participants' self-report of behavior problems were examined. Specifically, the three groups differed significantly on internalizing problems, but were comparable in externalizing and total behavior problems. The heterosexual desisters reported significantly lower internalizing problems compared to the bisexual/homosexual persisters and the bisexual/homosexual desisters. The two bisexual/homosexual groups were comparable on internalizing problems.

That the heterosexual desisters had, on average, less behavioral disturbance than the bisexual/homosexual persisters was also reflected in the percentage of participants in each group whose scores on internalizing, externalizing, and total problems fell within the clinical range. Across all three indices of disturbance, a greater proportion of the bisexual/homosexual persisters fell within the clinical range compared to the heterosexual desisters. Differences between the heterosexual desisters and bisexual/homosexual desisters were significant only on externalizing problems, with a greater proportion of the latter group falling within the clinical range. Across all three indices, there was no significant difference between the bisexual/homosexual persisters and bisexual/homosexual desisters on the percentage who fell within the clinical range.

Thus, the most consistent group differences on behavioral problems emerged between the bisexual/homosexual persisters and the heterosexual desisters, with the latter group reporting significantly less behavioral disturbance than the former. Less consistent was the group differences between the heterosexual desisters and bisexual/homosexual desisters. When differences did emerge, the heterosexual desisters reported less behavioral disturbance compared to the bisexual/homosexual desisters. At least on self-report of behavioral problems, the bisexual/homosexual persisters and bisexual/homosexual desisters were comparable.

The bisexual/homosexual persisters showed, on average, higher behavioral disturbance than nonreferred boys in the standardization sample when compared on the percentage in each group who fell within the clinical range on total problems on the YSR/ASR, but were comparable to referred boys. The bisexual/homosexual persisters had, on average, 5.18 times as many behavior problems compared with nonreferred boys. The percentage of heterosexual desisters who fell within the clinical range was lower than the referred boys in the standardization sample but comparable to nonreferred boys. The bisexual/homosexual desisters were comparable to the referred and nonreferred boys in the standardization sample.

4.10.2 Psychiatric Functioning at Follow-up

At follow-up, 37% of the entire group of participants did not have any comorbid psychiatric disorders, 23.1% had at least one, 17.7% had two, and 23.2% had three or more. Thus, 63% of participants had at least one comorbid psychiatric diagnosis at follow-up. The three outcome groups differed on the extent of psychiatric comorbidity at follow-up. Similar to the results obtained on behavioral problems at follow-up, the heterosexual desisters had

significantly fewer psychiatric diagnoses at follow-up compared to the bisexual/homosexual desisters and the bisexual/homosexual persisters. The bisexual/homosexual persisters and the bisexual/homosexual desisters were comparable on psychiatric comorbidity.

4.10.2.1 Implications of Psychiatric Outcomes

When group differences did emerge in behavioral problems and psychiatric functioning, the heterosexual desisters appeared less disturbed compared to the other groups. The bisexual/homosexual persisters and bisexual/homosexual desisters were generally comparable on behavioral problems and psychiatric functioning. Thus, there is evidence that behavioral and psychiatric problems at follow-up varied as a function of both gender identity and sexual orientation. As discussed below, a number of possible factors could account for these findings.

4.10.2.1.1 Distress of Gender Dysphoria

Applicants for sex reassignment often experience their gender dysphoria as unbearable (Cohen-Kettenis & Pfäfflin, 2010). It could be argued that gender dysphoria itself among the persisters was sufficiently distressing to these individuals and it caused secondary behavioral and psychiatric difficulties (Nuttbrock et al., 2010). Thus, the distress felt by adolescents with GID due to the incongruence between their gender identity and the physical characteristics of their biological sex (i.e., anatomic dysphoria) may itself have served as a vulnerability factor in the development of comorbid psychiatric issues (Zucker et al., 2012a). In some studies, however, transsexuals were not found to have had high rates of comorbid psychiatric diagnoses (e.g., Cole, O'Boyle, Emory, & Meyer, 1997; Gomez-Gil, Trilla, Salamero, Godas, & Valdes, 2009). In the clinical setting, some applicants for sex-reassignment surgery are employed, have relationships, and function socially without

problems. These individuals express that they suffer from incongruence between their anatomy and gender identity, but it does not interfere with their ability to function satisfactorily (Cohen-Kettenis & Pfäfflin, 2010). Cohen-Kettenis & Pfäfflin have interpreted this to mean that gender dysphoria, per se, may not necessarily be associated with psychiatric difficulties in some transgendered individuals. In the present study the bisexual/homosexual persisters and the bisexual/homosexual desisters were generally comparable on behavioral and psychiatric functioning, but when there were differences the bisexual/homosexual persisters had more difficulties than did the bisexual/homosexual desisters. Based on the hypothesis that gender dysphoria is sufficiently distressing to cause secondary behavioral and psychiatric difficulties (e.g., Nuttbrock et al., 2010), one would have expected more substantial differences between the bisexual/homosexual persisters and bisexual/homosexual desisters.

4.10.2.1.2 Peer and Family Rejection

Social rejection is another possible factor that could have contributed to the group differences on behavioral and psychiatric difficulties. Poor peer relations appear to be a general risk factor for behavior problems in children and youth (Schneider, 2000). Gender referred boys with GID experience substantial difficulties with peers (e.g., Zucker et al., 1997) and this has been found to be a significant predictor of CBCL behavior problems (Cohen-Kettenis et al., 2003). Although the quality of peer relation at follow-up was not measured in the present study, the results of other studies of GID adolescents suggest that these youth have significant problems with their peers (Zucker et al., 2012a). Retrospective studies of gay men had demonstrated that childhood gender nonconformity was significantly associated with peer rejection (Landolt, Bartholomew, Saffrey, Oram, & Perlman, 2004).

Although we did not have data on parental attitudes towards their child's gender dysphoria, it is possible that rejection from family members may have contributed to the elevated levels of behavioral and psychiatric disturbance among the bisexual/homosexual persisters compared to the heterosexual desisters. Transgendered adults, on average, may receive less social support from family members compared to their non-transgendered siblings (Factor & Rothblum, 2007) and among gay, lesbian, and bisexual youth, those who reported higher levels of familial rejection were at increased risk for psychological disturbance (suicide attempts, depression, substance use) compared to youth who reported no or low levels of family rejection (Ryan, Huebner, Diaz, & Sanchez, 2009). In future studies, it would be important to also measure levels of current support, at the peer and family level, in these individuals.

4.10.2.1.3 Minority Stress

Minority stress (i.e., social prejudice, victimization, and discrimination experienced by non-heterosexual individuals) appears to account, in part, for the strong association between homosexuality and mental health risk (Meyer, 1995; 2003). For example, within GLB populations, levels of mental health risk (e.g., suicidality, substance use) appear to be mediated by victimization (Almeida, Johnson, Corliss, Molnar, & Azrael, 2009; Bontempo & D'Augelli, 2002). In a study of 245 gay, lesbian, bisexual, and transgender youth (GLBT), victimization due to perceived or actual GLBT status fully mediated the association between gender nonconformity and psychosocial adjustment (Toomey, Ryan, Diaz, Card, & Russell, 2010). Thus, minority stress may be another factor that contributed to the higher rates of behavioral and psychiatric difficulties seen among the bisexual/homosexual persisters and bisexual/homosexual desisters. At the same time, studies of homosexual adults in countries

known for their liberal and accepting attitudes towards homosexuality, such as the Netherlands, also show a relationship between sexual orientation and mental health, with homosexual individual reporting more mental health difficulties compared to their heterosexual counterparts (e.g., Sandfort et al., 2006). In the present study, 62.5% of participants for whom data were available reported lifetime experience of victimization. As a group, participants' total victimization scores across their lifetime and in the 12 months preceding the follow-up assessment were significantly and positive correlated with a parent-report measure of concurrent cross-gender behavior. Thus, participants who were rated as more cross-gendered in behavior by their parents, had also self-reported higher levels of victimization compared to participants rated by their parents as having less cross-gendered behaviors. On an overall measure of victimization, the bisexual/homosexual persisters reported significantly more victimization in their lifetime and in the 12 months preceding the follow-up assessment compared to the bisexual/homosexual desisters and heterosexual desisters. Further, participants' overall victimization scores for the 12 months preceding the follow-up assessment were significantly and positively associated with their self-report of externalizing, and total problems on the Youth Self-Report/Adult Self-Report. Thus, participants who experienced higher levels of victimizations were more likely to report higher levels of emotional and behavioral problems.

These results are not surprising. Even among youth unselected for their gender identity, the presence of gender atypical behavior appears to be associated with poorer well being (Rieger & Savin-Williams, 2012) and places these youth at higher risk for victimization compared to gender atypical youth. Thus, transgender youth are particularly vulnerable to victimization because of their atypical gender role presentation (for a

discussion, see Stieglitz, 2010). Generally, the rates of victimization among transgender youth appear to be higher than the estimated rates for youth victimization in North American (e.g., Grossman, D'Augelli, & Salter, 2006; Nuttbrock et al., 2011).

Some sexual minority youth also struggle with felt stigma, defined as one's subjective experience of stigma against his/her group and this may influence decisions regarding disclosure of sexual orientation (Burn, Kadlec, & Rexer, 2005), and possibly gender identity. Self-stigmatization, also referred to as internalized homophobia, may influence individuals to conceal their sexual orientation and this may intensify their experienced minority stress and contribute to mental health difficulties (Oswalt & Wyatt, 2011). Self-stigmatization may have been operating among participants in the present study; however, this is speculative as this construct was not measured.

Sexual minority and transgender youth, on average, have been found to experience higher levels of psychological difficulties compared to their heterosexual and non-transgender counterparts, which is also supported by the results of the present study. One hypothesis for shared risk among these two groups is that the presence of gender atypical behavior in GID adolescents and homosexual men, rather than cross-gender identity or sexual orientation per se, places sexual and gender minority youth at risk. Rieger and Savin-Williams (2012) found some support for this hypothesis. In a study of 475 high school seniors, childhood and adolescent gender nonconformity was negatively associated with a measure of psychological well-being. This relationship was not moderated by sexual orientation. Thus, Rieger and Savin-Williams concluded that the factors that caused gender nonconforming homosexual or bisexual individuals to suffer psychologically may also apply to heterosexual individuals who are gender nonconforming. Savin-Williams and Ream

(2003) suggested that sexual orientation per se has little explanatory power for understanding the relatively consistent finding that homosexual individuals are at greater risk for mental health difficulties compared to their heterosexual counterparts; rather, the association exists within the social context in which gender atypical behavior and sexual orientation evoke negative reactions (e.g., victimization) that leads to psychological distress.

One can infer that the bisexual/homosexual persisters in the present study had more cross-gendered behavioral compared to the desisters by virtue of their persistent gender dysphoria. Parent-report of gender role behaviors at follow-up also supported this inference. The bisexual/homosexual persisters were rated as significantly more cross-gendered compared to both desister groups. The bisexual/homosexual desisters were, in turn, rated as more cross-gendered than the heterosexual desisters. Given the above discussions about the relationship between gender atypical behavior and mental health, this finding may, in part, account for the consistent finding that the heterosexual desisters in the present study were found to have had better behavioral and mental health outcomes at follow-up compared to the bisexual/homosexual persisters. One would have predicted that the bisexual/homosexual desisters would have had more behavioral and psychiatric difficulties than the heterosexual desisters but less than the bisexual/homosexual persisters but this was not consistently found.

4.10.2.1.4 Familial Psychiatric Vulnerability

The above summarized data are not to imply that victimization is the only factor that explains the increased risk for mental health problems in sexual minority individuals. There are likely other factors (Bailey, 1999). Mays and Cochran (2001) found that controlling for reported levels of discrimination among gay, lesbian, and bisexual adults reduced the relationship between sexual orientation and mental health but did not eliminate it. Similarly,

in a recent population based survey of Swedish adults, rates of depression, anxiety, and alcohol use were increased among individuals with same-sex sexual partners (Frisell, Lichtenstein, Rahman, & Langstrom, 2010). When discrimination and hate crime victimization were controlled for, this risk was reduced. However, controlling for familial factors in within-pair comparisons reduced and, at times, eliminated it. This suggests that the psychiatric vulnerability observed in sexual minority youth may also be understood from the perspective of more general familial risk.

Further support for the hypothesis that sexual minority youth may be psychiatrically vulnerable comes from a recent study of 4942 adult twin pairs which found that genetic factors accounted for 60% of the correlation between sexual orientation and depression (Zietsch et al., 2012). It is possible that the bisexual/homosexual persisters originated within families with higher levels of psychiatric difficulties and, therefore, had higher risk for developing such problems, compared to the heterosexual desisters. This is, of course, speculative as family psychiatric history was not systematically assessed.

4.11 Suicidality at Follow-up

One controversial mental health issue pertaining to sexual minority youth concerns suicidality ideation and suicide attempts (Zucker, 2010b). Gay, lesbian, and bisexual youth, in addition to being at greater risk for mental health disorders (e.g., Cochran, 2001; Meyer, 2003), are also at greater risk for suicidal behaviors (Halpert, 2002; Kulkin, Chauvin, & Percle, 2000) compared to heterosexual counterparts. In a recent meta-analysis, King et al. (2008) concluded that sexual minorities were 2.47 times more likely to have attempted suicide in their lifetime. Further, high rates of suicide attempts among sexual minority individuals does not appear to simply be an artifact of high rates of mental disorder in this

group, but, rather, occurs independent of psychiatric diagnosis at higher rates than heterosexual individuals (Bolton & Sareen, 2011). Although epidemiological studies have not been conducted, available data on transgendered youth using community samples suggest a greater risk for suicidal ideation and self harm (e.g., Almeida et al., 2009; Mathy, 2003) compared to non-transgendered youth. That there is elevated risk for suicidality among homosexual and transgendered youth was supported by results of the present study.

On the Suicidality Questionnaire, the three outcome groups differed significantly on number of lifetime suicide attempts. The bisexual/homosexual desisters reported, on average, a greater number of lifetime suicide attempts compared to the heterosexual desisters but were comparable to the bisexual/homosexual persisters.

Suicidal ideation in the 6 months preceding the follow-up assessment was measured using the Youth Self Report (YSR)/Adult Self Report (ASR). The bisexual/homosexual persisters were significantly more likely to endorse this item compared to the heterosexual desisters, but were comparable to the bisexual/homosexual desisters. The frequency of reported suicidal ideation among the bisexual/homosexual persisters was also significantly higher than that reported by referred and nonreferred boys in the YSR standardization sample and the nonreferred boys in the ASR standardization sample. The bisexual/homosexual desisters were more likely to endorse suicidal ideation compared to the nonreferred boys in the YSR and ASR standardization samples but were comparable to referred boys. The results for the heterosexual desisters varied according to the standardization sample used for comparison—group differences only emerged when compared to the ASR standardization sample. The heterosexual desisters were more likely to endorse suicidal ideation compared to the nonreferred boys but were less likely to when compared to the referred boys. Thus, the

bisexual/homosexual persisters were the only group who reported greater suicidal ideation when compared to a group of clinically referred boys.

The three outcome groups also differed on suicidal and self-harm behavior⁶² in the 6 months preceding the follow-up assessment. The bisexual/homosexual persisters were significantly more likely to endorse suicidal and self-harm behaviors compared to the bisexual/homosexual desisters, heterosexual desisters, referred boys in the standardization sample, and non-referred boys in the YSR and ASR standardization samples. The heterosexual desisters reported significantly more suicidal behavior compared to the nonreferred boys in the YSR standardization sample only, but were comparable to the bisexual/homosexual desisters and to referred boys in both standardization sample. The bisexual/homosexual desisters reported less suicidal behavior compared to the referred boys in the ASR standardization sample only, but were comparable to the nonreferred boys from both standardization samples. Thus, the most consistent finding from the YSR/ASR suicidality data was that the bisexual/homosexual persisters were significantly more likely to have experienced suicidal ideation and suicidal and self-harm behaviors compared to the other groups, including the standardization samples. However, in terms of lifetime risk of suicide attempts, the bisexual/homosexual desisters reported the highest number.

Studies of community samples of transgendered youth have suggested that they may be at even greater risk for suicide ideation and attempts than homosexual males (Mathy,

⁶² Recent studies using community samples of youth suggest that rates of self-harm behaviors, including non-suicidal self-injurious behaviors, is a growing health concern and may be higher than rates of suicidal ideation and attempt (e.g., Jacobson & Gould, 2007). Growing concern about the high rates of self-harm behaviors among youth had led DSM-5 work groups to consider the possibility of defining non-suicidal self-injury as a distinct syndrome (Glenn & Klonsky, 2010). In the present study, suicidal behavior and self-harm were not measured as separate constructs and, therefore, may represent a limitation. However, one goal of the study was to obtain general outcomes with regard to suicidality, defined broadly to include self-harm behaviors. Future studies would be needed to determine if there are unique risks for suicidal behavior and non-suicidal self-harm within this population and whether different psychosexual outcomes are associated with different risks for suicidality vs. non-suicidal self-harm behaviors.

2003) and that cross-gender role behavior may be responsible for these findings (Maugen & Shipherd, 2010). Thus, while some homosexual men may engage in gender atypical behaviors that place them at risk, the pervasive and more extreme cross-gender behaviors of transgendered individuals may place them at even higher risk compared to homosexual individuals. In one study, cross-gender role accounted for more of the variance in suicidal ideation than sexual orientation (Fitzpatrick, Euton, Jones, & Schmidt, 2005) and in another study of gay, lesbian, and bisexual adults, the relationship between sexual orientation and suicidality decreased substantially after gender atypical behaviors were controlled for (Plöderl & Fartacek, 2009). The greater risk for suicidal ideation and attempts among transgendered youth compared to homosexual (and heterosexual) youth may be directly related to discrimination and victimization pertaining to their atypical gender role behaviors (Clements-Nolle et al., 2006; Nuttbrock, 2010). In a recent prospective study of 246 gay, lesbian, bisexual, and transgendered youth, victimization was associated with both suicidal ideation and self-harm, as was a history of completed suicide (Liu & Mustanski, 2012). In a study of 55 transgendered youth recruited from programs that provide services to this population, Grossman and D'Augelli (2007) attempted to clarify what differences might exist between those who attempted suicide and those who did not along the parameters of gender nonconformity, childhood parental abuse, body self esteem, and negative thoughts about transgendered identity. The suicide attempters reported greater parental abuse, more negative body self-esteem, and more negative thoughts about being transgendered compared to the non-attempters. Thus, it is possible that, in addition to minority stress and victimization, there are additional factors that contribute to the elevated risk for suicidality among transgendered youth, including factors discussed above that are deemed relevant to understanding elevated

risk for mental health issues within this population, including gender dysphoria itself, and general familial risk.

It has been an assumption that gender dysphoria itself is one reason for the increased prevalence of suicidality among transgendered youth. However, follow-up data on psychiatric outcome of transgendered individuals who receive cross-sex hormonal therapy and sex-reassignment surgery suggest that, even among individuals who receive medical treatment for gender dysphoria, there may be an increased risk for suicidality compared to the general population (Asscheman et al., 2011; Dhejne et al., 2011; van Kesteren, Asscheman, Megens, & Gooren, 1997). These findings are surprising as one would expect that sex-reassignment surgery, which will serve to align the body of transgendered individuals with their gender identity, would substantially reduce the gender dysphoria, if not eliminate it, and, therefore, reduce the risk for suicide. Continued risk for suicidality suggests that there may be an underlying vulnerability for suicidality (and, perhaps, depression more generally) that contributes to its persistence even after medical treatment for gender dysphoria is received.

In a recent three-part video series called “The Sissy Boy Experiment,” CNN’s Anderson Cooper reported on Kirk Murphy, who committed suicide in 2003 when he was 38-years-old. Kirk was one of the “feminine” boys in Green’s (1987) follow-up study. Following Kirk’s childhood assessment, he was seen in therapy by George Rekers at the University of California, Los Angeles (UCLA). A published report of Kirk’s treatment⁶³ (Rekers & Lovaas, 1974) indicated that a behavioral approach had “normalized” Kirk’s sex-typed behaviors and “he looked and acted like any other boy.” At follow-up, when he was

⁶³ Kirk was given the pseudonym “Kraig” in Rekers and Lovaas’ (1974) treatment report. He was referred to as “Kyle” in Green (1987).

18-years-old, Kirk identified as a male and was happy with his gender identity. He reported a bisexual sexual orientation.

In “The Sissy Boy Experiment,” the viewer finds out that Kirk later disclosed a homosexual sexual orientation. This case report and above summarized data on psychiatric functioning have three important implications. First, even after receiving treatment for gender dysphoria, transgendered individuals appear to be at risk for suicidality/psychiatric difficulties. Second, prospective studies should follow these individuals beyond adolescence and well into adulthood. On this point, a recent study of 571 male-to-female transgender individuals⁶⁴ recruited from the population found a prevalence rate of depression to be 54.3%. When examined according to age group, the highest levels of depression were found among those aged 19-39 years, and then decreased thereafter (Nuttbrock et al., 2010). Third, children with GID who later desist in their gender dysphoria may still be psychiatrically vulnerable. In the present study, the bisexual/homosexual desisters reported the highest rate of lifetime suicide attempts and the heterosexual desisters reported significantly more suicidal and self-harm behaviors compared to nonreferred boys in the standardization samples. A general implication of these findings is that, in practice, clinicians working with youth should ask about sexual orientation, given the strong relationship between minority orientation and psychiatric problems and suicidality.

4.12 Limitations of the Present Study and Future Directions

The most prominent limitation of the study is that concurrent control groups, either clinical (i.e., referred for reasons other than gender identity concerns) or community, were not employed. Accordingly, some of the comparative analyses relied on epidemiological or

⁶⁴ It is unclear whether the participants in the study were pre sex reassignment surgery, post sex reassignment surgery, or a combination of both.

survey data. However, the exclusion of a control group is methodologically justified given the goal of the study was to examine outcomes within a specific group of children.

There are a number of prospective approaches that can be used study the relationship between cross-gender behavior in childhood and later gender identity and sexual orientation, and with each approach there are implications on the populations to which results can be generalized. This present study examined children referred to a specialized gender identity clinic because of concern around their cross-gender behavior and gender identity status. Therefore, generalizations about psychosexual development and psychiatric functioning in adolescence and adulthood are limited to clinic-referred boys with severe cross-gender behaviors. Generalizations to other populations should be done with caution.

There were a number of other factors which may affect the long-term psychosexual outcome of boys with GID which were not evaluated in the present study. A major such factor pertains to the role of psychotherapy on long-term psychosexual and psychiatric outcomes. Future studies which systematically evaluate treatment involvement and utilizing relevant comparison groups will provide much needed information regarding the differential effects of various treatment options, including no treatment, on long-term outcomes. These data are urgently needed given the lack of treatment consensus within the field.

Although this study has contributed substantially towards understanding childhood predictors of outcome within a group of boys with GID, as a field, we do not understand how and when desistence of gender dysphoria occurs. Systematic prospective studies, utilizing multiple follow-up assessments that extend well into early adulthood are needed.

Data on continued risk for suicidality in transgendered youth and among boys with GID who desist in their gender dysphoria as well as the empirical literature on the coming

out process suggest that follow-up periods should ideally extend beyond adolescence and into adulthood.

4.13 Conclusion

Since Green and Money's (1960) seminal article on boys with "incongruous gender role," much progress has been made in understanding the phenomenology of GID. The long-term psychosexual outcome of boys with GID has also received some empiric attention, with studies having consistently found that most boys desisted in their gender dysphoria and had a homosexual sexual orientation. The present study extended previous follow-up studies of boys with GID and, in addition to examining rates of persistent gender dysphoria and sexual orientation outcome, attempted to identify within-group childhood factors that were predictive of long-term psychosexual outcomes. In the present follow-up study, the most common outcome at follow-up, consistent with the extant literature, was a desistence of GID with a co-occurring bisexual/homosexual sexual orientation. Childhood social economic status and severity of cross-gender behavior were identified as predictors of long-term gender identity outcome. Notwithstanding these empirical gains, a number of questions were still left unresolved. We still do not understand the process through which GID desists. We also do not understand how psychosocial factors interact with the very likely biological predisposition for cross-gender identity/behavior to influence long-term outcome. The role of therapeutics on outcome also remains unclear. It is hoped that future studies will examine the effects, if any, of different therapeutic approaches on persistence and desistence of GID. The present study was the first to systematically assess psychiatric functioning at follow-up. Future follow-up studies should incorporate longer follow-up periods that extend well into

adulthood as adolescents and adults with GID appeared to be a psychiatrically vulnerable group, even if the gender dysphoria desists.

References

- Achenbach, T. M. (1985). *Assessment and taxonomy of child and adolescent psychopathology*. Thousand Oaks, CA: Sage Publications.
- Achenbach, T. M. (1991). *Manual for the child behavior checklist/4-18 and 1991 profile*. Burlington, VT: University of Vermont Department of Psychiatry.
- Achenbach, T. M. (1997). *Manual for the Young Adult Self Report and Young Adult Behavior Checklist*. Burlington, VT: University of Vermont, Department of Psychiatry.
- Achenbach, T. M., & Edelbrock, C. (1983). *Manual for the child behavior checklist and revised child behavior profile*. Burlington, VT: University of Vermont, Department of Psychiatry.
- Achenbach, T. M., & Edelbrock, C. (1986). *Manual for the Youth Self-Report and Profile*. Burlington, VT: University of Vermont, Department of Psychiatry.
- Achenbach, T. M., Howell, C. T., McConaughy, S. H., & Stanger, C. (1995). Six year predictors of problems in a national sample III: Transitions to young adult syndromes. *Journal of the American Academy of Child and Adolescent Psychiatry*, 34, 658-669.
- Achenbach, T. M., Krukowski, R. A., Dumenci, L., & Ivanova, M. Y. (2005). Assessment of adult psychopathology: Meta-analyses and implications of cross-informant correlations. *Psychological Bulletin*, 131, 361-382.
- Achenbach, T. M., McConaughy, S. H., & Howell, C. T. (1987). Child/adolescent behavior and emotional problems: Implications of cross-informant correlations for situational specificity. *Psychological Bulletin*, 101, 213-232.

Achenbach, T. M., & Rescorla, L. A. (2003). *Manual for ASEBA Adult Forms & Profiles*.

Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Alanko, K., Santtila, P., Harlaar, N., Witting, K., Varjonen, M., Jern, P., ..., & Sandnabba, N.

K. (2010). Common genetic effects of gender atypical behavior in childhood and sexual orientation in adulthood: A study of Finnish twins. *Archives of Sexual Behavior*, 39, 81-92.

Alexander, G. M., & Hines, M. (1994). Gender labels and play styles: Their relative contribution to children's selections of playmates. *Child Development*, 65, 869-879.

Almeida, J., Johnson, R. M., Corliss, H. L., Molnar, B. E., & Azrael, D. (2009). Emotional distress among LGBT Youth: The influence of perceived discrimination based on sexual orientation. *Journal of Youth and Adolescence*, 38, 1001-1014.

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: Author.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

Asscheman, H., Giltay, E. J., Megens, J. A. J., de Ronde, W. P., van Trotsenburg, A. A., & Gooren, L. J. G. (2011). A long-term follow-up study of mortality in transsexuals

receiving treatment with cross-sex hormones. *European Journal of Endocrinology*, 164, 635-642.

Anduaga, J. C., Forteza, C. G., & Lira, L. R. (1991). Concurrent validity of the DIS: Experience with psychiatric patients in Mexico City. *Hispanic Journal of Behavioral Sciences*, 13, 63-77.

Ault, A., & Brzuzny, S. (2009). Commentary: Removing gender identity disorder from the Diagnostic and Statistical Manual of Mental Disorders: A call for action. *Social Work*, 54, 187-189.

Bailey, J. M. (1999). Homosexuality and mental illness. *Archives of General Psychiatry*, 56, 883-884.

Bailey, J. M. (2009). What is sexual orientation and do women have one? In: Hope, D. A. (Series Ed.), *Nebraska symposium on motivation: Vol. 54. Contemporary perspectives on lesbian, gay, and bisexual identities (pp. 43-64)*. New York: Springer.

Bailey, J. M., & Bell, A. P. (1993). Familiality of female and male homosexuality. *Behavior Genetics*, 23, 313-322.

Bailey, J. M., Bobrow, D., Wolfe, M., & Mikach, S. (1995). Sexual orientation of adult sons of gay fathers. *Developmental Psychology*, 31, 124-129.

Bailey, J. M., Dunne, M. P., & Martin, N. G. (2000). Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample. *Journal of Personality and Social Psychology*, 78, 524-536.

Bailey, J. M., Kim., P. Y., Hills, A., & Linsenmeier, J. A. (1997). Butch, femme, or straight acting? Partner preferences of gay men and lesbians. *Journal of Personality and Social Psychology*, 73, 960-973.

- Bailey, J. M., Miller, J. S., & Willerman, L. (1993). Maternally rated gender nonconformity in homosexuals and heterosexuals. *Archives of Sexual Behavior*, 22, 461-469.
- Bailey, J. M., Nothnagel, J., & Wolfe, M. (1995). Retrospectively measured individual differences in childhood sex-typed behaviour among gay men: Correspondence between self- and maternal reports. *Archives of Sexual Behavior*, 24, 613-622.
- Bailey, J. M., & Oberschneider, M. (1997). Sexual orientation and professional dance. *Archives of Sexual Behavior*, 26, 433-444.
- Bailey, J. M., & Pillard, R. C. (1991). A genetic study of male sexual orientation. *Archives of General Psychiatry*, 48, 1089-1096.
- Bailey, J. M., & Pillard, R. C. (1995). Genetics of human sexual orientation. *Annual Review of Sex Research*, 6, 126-150.
- Bailey, J. M., Pillard, R. C., Dawood, K., Miller, M. B., Farrer, L. A., Trivedi, S., & Murphy, R. L. (1999). A family history of male sexual orientation. *Behavior Genetics*, 29, 79-86.
- Bailey, J. M., Willerman, L., & Parks, C. (1991). A test of the maternal stress theory of human male homosexuality. *Archives of Sexual Behavior*, 20, 277-293.
- Bailey, J. M., & Zucker, K. J. (1995). Childhood sex-typed behaviour and sexual orientation: A conceptual analysis and quantitative review. *Developmental Psychology*, 1, 43-55.
- Bakker, A., van Kesteren, P. J. M., Gooren, L. J. G., & Bezemer, P. D. (1993). The prevalence of transsexualism in the Netherlands. *Acta Psychiatrica Scandinavica*, 87, 237-238.
- Bakwin, H. (1968). Deviant gender-role behavior in children: Relation to homosexuality. *Pediatrics*, 41, 620-629.

- Barber, M. E. (2000). Examining differences in sexual expression and coming out between lesbians and gay men. *Journal of the Gay and Lesbian Medical Association*, 4, 167-174.
- Bartlett, N. H., & Vasey, P. L. (2006). A retrospective study of childhood gender-atypical behavior in Samoan fa'afafine. *Archives of Sexual Behavior*, 35, 559-566.
- Bartlett, N. H., Vasey, P. L., & Bukowski, W. M. (2000). Is gender identity disorder in children a mental disorder? *Sex Roles*, 43, 753-785.
- Bates, J. E., Skilbeck, W. M., Smith, K. V. R., & Bentler, P. M. (1974). Gender role abnormalities in boys: An analysis of clinical ratings. *Journal of Abnormal Child Psychology*, 2, 1-16.
- Beaty, L. A. (1999). Identity development of homosexual youth and parental and family influences on the coming out process. *Adolescence*, 34, 597-601.
- Beautrais, A. L. (2003). Suicide and serious suicide attempts in youth: A multiple-group comparison study. *American Journal of Psychiatry*, 160, 1093-1099.
- Bem, D. J. (1996). Exotic becomes erotic: A developmental theory of sexual orientation. *Psychological Review*, 103, 320-335.
- Bem, D. J. (2008). The exotic becomes erotic: A review of theory and research. *Journal of Gay & Lesbian Mental Health*, 12, 61-79.
- Berenbaum, S. A. (1999). Effects of early androgens on sex-typed activities and interests in adolescents with congenital adrenal hyperplasia. *Hormones and Behavior*, 35, 102-110.
- Berenbaum, S. A., & Hines, M. (1992). Early androgens are related to childhood sex-typed toy preferences. *Psychological Science*, 2, 203-206.

- Berenbaum, S. A., & Snyder, E. (1995). Early hormonal influences on childhood sex-typed activity and playmate preferences: Implications for the development of sexual orientation. *Developmental Psychology, 1*, 31-42.
- Berrill, K. (1990). Anti-gay violence and victimization in the United States: An overview. *Journal of Interpersonal Violence, 5*, 274-294.
- Blakemore, J. E. O. (2003). Children's beliefs about violating gender norms: Boys should look like girls, and girls shouldn't act like boys. *Sex Roles, 48*, 411-419.
- Bockting, W. O. (1997). The assessment and treatment of gender dysphoria. *Directions in Clinical and Counselling Psychology, 7*, 1-22.
- Bockting, W. O. (2009). Are gender identity disorders mental disorders? Recommendations for revision of the World Professional Association for Transgender Health's Standards of Care. *International Journal of Transgenderism, 11*, 53-62.
- Bockting, W. O., & Ehrbar, R. D. (2005). Commentary: Gender variance, dissonance, or identity disorder? *Journal of Psychology & Human Sexuality, 17*, 125-134.
- Bodlund, O., & Armelius, K. (1994). Self-image and personality traits in gender identity disorders: An empirical study. *Journal of Sex & Marital Therapy, 20*, 303-317.
- Boegart, A. F. (2003). Interaction of older brothers and sex-typing in the prediction of sexual orientation in men. *Archives of Sexual Behavior, 32*, 129-134.
- Bolton, S.-L., & Sareen, J. (2011). Sexual orientation and its relation to mental disorders and suicide attempts: Findings from a nationally representative sample. *The Canadian Journal of Psychiatry, 56*, 35-43.

- Bontempo, D. E., & D'Augelli, A. R. (2002). Effects of at-school victimization and sexual orientation on lesbian, gay, or bisexual youths' health risk behaviour. *Society for Adolescent Medicine*, 30, 364-374.
- Bower, H. (2001). The gender identity disorders in the DSM-IV classification: A critical evaluation. *Australian and New Zealand Journal of Psychiatry*, 35, 1-8.
- Bradley, R. H., & Corwyn, R. F. (2002). Socioeconomic status and child development. *Annual Review of Psychology*, 53, 371-399.
- Bradley, S. J. (1998). Assessment of sexual and gender development in adolescents. In S. I. Harrison & S. Eth (Eds.), *Handbook of child and adolescent psychiatry* (pp. 252-258). New York: John Wiley & Sons.
- Bradley, S. J. (1999). Gender dysphorias of childhood and adolescence. In B. D. Garfinkel, G. A. Carlson, & E. B. Weller (Eds.), *Psychiatric disorders in children and adolescents* (pp. 121-134). Philadelphia: Saunders
- Bradley, S. J., Blanchard, R., Coates, S., Green, R., Levine, S. B., Meyer-Bahlburg, H. F. L.,...Zucker, K. J. (1991). Interim report of the DSM-IV Subcommittee on Gender Identity Disorders. *Archives of Sexual Behavior*, 20, 333-343.
- Bradley, S. J., & Zucker, K. J. (1997). Gender identity disorder: A review of the past 10 years. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36, 872-880.
- Bradley, S. J., & Zucker, K. J. (1998). Gender identity disorder [Letter to the Editor]. *Journal of the American Academy of Child and Adolescent Psychiatry*, 37, 244-246.

- Bradley, S. J., & Zucker, K. J. (2003). Children with gender nonconformity [Letter to the Editor]. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42, 266-268.
- Brender, N. C., Kann, L., McManus, T., Kinchen, S. A., Sundberg, E. C., & Ross, J. G. (2002). Reliability of the 1999 Youth Risk Behavior Survey Questionnaire. *Journal of Adolescent Health*, 31, 336-342.
- Brill, S., & Pepper, R. (2008). *The transgender child: A handbook for families and professionals*. San Francisco, CA: Cleis Press.
- Brown, P. L. (2006, December 2). Supporting boys or girls when the line isn't clear. *New York Times*, pp. A1, A11.
- Bryant, K. (2006). Making gender identity disorder of childhood: Historical lessons for contemporary debates. *Sexuality Research and Social Policy*, 3, 23-39.
- Burn, S. M., Kadlec, K., & Rexer, R. (2005). Effects of subtle heterosexism on gays, lesbians, and bisexuals. *Journal of Homosexuality*, 49, 23-38.
- Campbell, D. T., & Stanley, J. C. (1963). *Experimental and quasi-experimental designs for research*. Chicago: Rand McNally & Company.
- Cardoso, F. L. (2009). Recalled sex-typed behavior in childhood and sports' preferences in adulthood of heterosexual, bisexual, and homosexual men from Brazil, Turkey, and Thailand. *Archives of Sexual Behavior*, 38, 726-736.
- Carlson, G. A., Kashani, J. H., Thomas, M. D. F., Vaidya, A., & Daniel, A. E. (1987). Comparison of the DISC and the K-SADS interviews in an epidemiological sample of children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 26, 645-648.

- Caron, C., & Rutter, M. (1991). Comorbidity in child psychopathology: Concepts, issues, and research strategies. *Journal of Child Psychology and Psychiatry*, 32, 1063-1080.
- Carrier, J. M. (1986). Childhood cross-gender behavior and adult homosexuality [Letter to the Editor]. *Archives of Sexual Behavior*, 15, 89-93.
- Carver, P. R., Yunger, J. L., & Perry, D. G. (2003). Gender identity and adjustment in middle school. *Sex Roles*, 49, 95-109.
- Centers for Disease Control. (2002). Trends in sexual risk behaviors among high school students-United States, 1991-2001. *Mortality of Morbidity Weekly Reviews*, 51, 856-859.
- Chivers, M. L., Rieger, G., Latty, E., & Bailey, J. M. (2004). A sex difference in the specificity of sexual arousal. *Psychological Science*, 15, 736-744.
- Cicchetti, D., & Rogosch, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology*, 8, 597-600.
- Clements-Nolle, K., Marx, R., & Katz, M. (2006). Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *Journal of Homosexuality*, 51, 53-69.
- Coates, S., & Person, E. S. (1985). Extreme boyhood femininity: Isolated behavior or pervasive disorder? *Journal of the American Academy of Child Psychiatry*, 24, 702-709.
- Coates, S., & Wolfe, S. (1997). Gender identity disorders of childhood. In J. D. Noshpitz (Ed.) and S. Greenspan, S. Wieder, & J. Osofsky (Vol. eds.), *Handbook of child and adolescent psychiatry: Vol. I. Infants and preschoolers: Development and syndromes* (pp. 453-472). New York: Wiley.
- Cochran, S. D. (2001). Emerging issues in research on lesbians' and gay men's mental health: Does sexual orientation really matter? *American Psychologist*, 56, 931-947.

- Cochran, S. D., & Mays, V. M. (2000). Lifetime prevalence of suicide symptoms and affective disorders among men reporting same-sex sexual partners: Results from NHANES III; *American Journal of Public Health*, 90, 573-578.
- Cochran, S. D., Sullivan, J. G., & Mays, V. M. (2003). Prevalence of mental disorders, psychological distress, and mental health services use among lesbian, gay and bisexual adults in the United States. *Journal of Consulting and Clinical Psychology*, 71, 53-61.
- Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.) Hillsdale, NJ: Erlbaum.
- Cohen, K. M. (2002). Relationships among childhood sex-atypical behavior, spatial ability, handedness, and sexual orientation in men. *Archives of Sexual Behavior*, 31, 129-143.
- Cohen-Kettenis, P. T. (2001). Gender identity disorder in DSM? [Letter to the Editor]. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40, 391.
- Cohen-Kettenis, P. T., Delemarre-van de Waal, H. A., & Gooren, L. J. G. (2008). The treatment of adolescent transsexuals: Changing insights. *Journal of Sexual Medicine*, 5, 1892-1897.
- Cohen-Kettenis, P. T., & Gooren, L. J. G. (1999). Transsexualism: A review of etiology, diagnosis, and treatment. *Journal of Psychosomatic Research*, 46, 315-333.
- Cohen-Kettenis, P. T., Owen, A., Kaijser, V. G., Bradley, S. J., & Zucker, K. J. (2003). Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: A cross-national, cross-clinic comparative analysis. *Journal of Abnormal Psychology*, 112, 41-53.
- Cohen-Kettenis, P. T., & Pfäfflin, F. (2003). *Transgenderism and intersexuality in childhood and adolescence: Making choices*. Thousand Oaks, CA: Sage.

- Cohen-Kettenis, P. T., & Pfäfflin, F. (2010). The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Archives of Sexual Behavior*, 39, 499-513.
- Cohen-Kettenis, P. T., & van Goozen, S. H. M. (1997). Sex reassignment of adolescent transsexuals: A follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36, 263-271.
- Cohen-Kettenis, P. T., Wallien, M., Johnson, L. L., Owen-Anderson, A. F. H., Bradley, S. J., & Zucker, K. J. (2006). A parent-report Gender Identity Questionnaire for children: A cross-national, cross-clinic comparative analysis. *Clinical Child Psychology and Psychiatry*, 7, 433-456.
- Cole, C. M., O'Boyle, M., Emory, L. E., & Meyer, W. J. (1997). Comorbidity of gender dysphoria and other major psychiatric diagnoses. *Archives of Sexual Behavior*, 26, 13-26.
- Compton, W. M., & Cottler, L. B. (2004). The Diagnostic Interview Schedule (DIS). In M. Hersen (Ed.) and M. Hilsenroth, & D. L. Segal (Vol. eds.), *Personality assessment, Vol. 2: Comprehensive handbook of psychological assessment* (pp. 153-162). Hoboken, NJ: Wiley.
- Corbett, K. (1998). Cross-gendered identifications and homosexual boyhood: Toward a more complex theory of gender. *American Journal of Orthopsychiatry*, 68, 352-360.
- Clements-Nolle, K., Marx, R. & Katz, M. (2006). Attempted suicide among transgendered persons: The influence of gender based discrimination and victimization. *Journal of Homosexuality*, 51, 53-69.
- Crowne, D. P., & Marlowe, D. (1960). A new scale of social desirability independent of psychopathology. *Journal of Consulting Psychology*, 24, 349-354.

- Dalsgaard, S., Mortensen, P. B., Frydenberg, M., & Thomsen, P. H. (2002). Conduct problems, gender, and adult psychiatric outcome of children with attention-deficit hyperactivity disorder. *British Journal of Psychiatry*, 181, 416-421.
- Dascalu, M., Compton, W.M., Horton, J. C., & Cottler, L. B. (2001). Validity of DIS-IV in diagnosing depression and other psychiatric disorders among substance users. *Drug and Alcohol Dependence*, 63(S), 37.
- D'Augelli, A. R. (2002). Mental health problems among lesbian, gay, and bisexual youths ages 14-21. *Clinical Child Psychology and Psychiatry*, 7, 433-456.
- D'Augelli, A. R. (2006). Developmental and contextual factors and mental health among lesbian, gay, and bisexual youths. In A. M. Omoto & H. S. Kurtzman (Eds.), *Sexual orientation and mental health: Examining identity and development in lesbian, gay, and bisexual people* (pp. 37-54). Washington, DC: American Psychological Association.
- D'Augelli, A. R., & Grossman, A. H. (2001). Disclosure of sexual orientation, victimization, and mental health among lesbian, gay, and bisexual older adults. *Journal of Interpersonal Violence*, 16, 1008-1027.
- D'Augelli, A. R., & Hershberger, S. L. (1993). Lesbian, gay, and bisexual youth in community settings: Personal challenges and mental health problems. *American Journal of Community Psychology*, 21, 421-448.
- D'Augelli, A. R., Hershberger, S. L., & Pilkington, N. W. (1998). Lesbian, gay, and bisexual youth and their families: Disclosure of sexual orientation and its consequences. *American Journal of Orthopsychiatry*, 68, 361-371.

- D'Augelli, A. R., Hershberger, S. L., & Pilkington, N. W. (2001). Suicidality patterns and sexual orientation-related factors among lesbian, gay, and bisexual youths. *Suicide and Life-Threatening Behavior*, 31, 250-264.
- D'Augelli, A. R., Pilkington, N. W., & Hershberger, S. L. (2002). Incidence and mental health impact of sexual orientation victimization of lesbian, gay, and bisexual youths in high school. *School Psychology Quarterly*, 17, 148-167.
- Davenport, C. W. (1986). A follow-up study of 10 feminine boys. *Archives of Sexual Behavior*, 15, 511-517.
- De Cuypere, G., Jannes, C., & Rubens, R. (1995). Psychosocial functioning of transsexuals in Belgium. *Acta Psychiatrica Scandinavica*, 91, 180-184.
- De Cuypere, G. T., T'Sjoen, G., Beerten, R., Selvaggi, G., De Sutter, P., Hoebeke, P.,...Rubens, R. (2007). Sexual and physical health after sex reassignment surgery. *Archives of Sexual Behavior*, 34, 679-690.
- De Cuypere, G. T., Van Hemelrijck, M., Michel, A., Carael, B., Heylens, G., Rubens, R.,...Monstrey, S. (2007). *Prevalence and demography of transsexualism in Belgium. European Psychiatry*, 22, 137-141.
- Dessens, A. B., Slijper, F. M. E., & Drop, S. L. S. (2005). Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Archives of Sexual Behavior*, 34, 389-397.
- de Vries, A. L. C., & Cohen-Kettenis, P. T. (2012). Clinical management of gender dysphoria in children and adolescents: The Dutch approach. *Journal of Homosexuality*, 59, 301-320.

de Vries, A. L. C., Doreleijers, T. A., Steensma, T. D., & Cohen-Kettenis, P. T. (2011b).

Psychiatric comorbidity in gender dysphoric adolescents. *Journal of Child Psychology and Psychiatry*, 52, 1195-1202.

de Vries, A. L. C., Noens, I. L., Cohen-Kettenis, P. T., van Berckelaer-Onnes, I. A., &

Doreleijers, T. A. H. (2010). Autism spectrum disorders in gender dysphoric children and adolescents. *Journal of Autism and Developmental Disorders*, 40, 930-936.

de Vries, A. L. C., Steensma, T. D., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2011a).

Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. *Journal of Sexual Medicine*, 8, 2276-2283.

Deogracias, J. J., Johnson, L. L., Meyer-Bahlburg, H. F. L., Kessler, S. J., Schober, J. M., &

Zucker, K. J. (2007). The Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults. *Journal of Sex Research*, 44, 370-379.

Dhejne, C., Lichtenstein, P., Boman, M., Johansson, A. L. V., Långström, N., & Lande, N.

(2011). Long-term follow-up of transsexual persons undergoing sex reassignment surgery: Cohort study in Sweden. *PLoS One*, 6, e16885.

Diamond, M. (1993). *Homosexuality and bisexuality in different populations. Archives of Sexual Behavior*, 22, 291-310.

Diamond, L. M. (2000). Sexual identity, attractions, and behavior among young sexual-minority women over a 2-year period. *Developmental Psychology*, 36, 241-250.

Diamond, M. (2002). Sex and gender are different: Sexual identity and gender identity are different. *Clinical Child Psychology and Psychiatry*, 7, 320-334.

Dreger, A. (2009). Gender identity disorder in children: Inconclusive advice to parents.

Hastings Center Report, 39, 26-29.

- Drescher, J. (2010a). Queer diagnoses: Parallels and contrasts in the history of homosexuality, gender variance, and the *Diagnostic and Statistical Manual*. *Archives of Sexual Behavior*, 39, 427-460.
- Drescher, J. (2010b). Transsexualism, gender identity disorder and the DSM. *Journal of Gay & Lesbian Mental Health*, 14, 109-122.
- Drescher, J., & Byne, W. (2012). Gender dysphoric/gender variant (GD/DV) children and adolescents: Summarizing what we know and what we have yet to learn. *Journal of Homosexuality*, 59, 501-510.
- Drummond, K. D. (2006). *A follow-up study of girls with gender identity disorder*. Unpublished master's thesis, Ontario Institute for Studies in Education of the University of Toronto, Toronto, Ontario, Canada.
- Drummond, K. D., Bradley, S. J., Peterson-Badali, M., & Zucker, K. J. (2008). A follow-up study of girls with gender identity disorder. *Developmental Psychology*, 44, 34-45.
- Edwards-Leeper, L., & Spack, N. P. (2012). Psychological evaluation and medical treatment of transgender youth in an interdisciplinary "Gender Management Service" (GeMS) in a major pediatric center. *Journal of Homosexuality*, 59, 321-336.
- Egan, S. K., & Perry, D. G. (2001). Gender identity: A multidimensional analysis with implications for psychosocial adjustment. *Developmental Psychology*, 37, 451-463.
- Ehrensaft, D. (2011). "I'm a Prius": A child case of a gender/ethnic hybrid. *Journal of Gay & Lesbian Mental Health*, 15, 46-57.
- Ehrensaft, D. (2012). From gender identity disorder to gender identity creativity: True gender self child therapy. *Journal of Homosexuality*, 59, 337-356.

English, B. (2011, December). Led by the child who simply knew. *The Boston Globe*.

Retrieved January 07, 2012 from www.bostonglobe.com.

Erlenmeyer-Kimling, L., Adamo, U. H., Rock, D., Roberts, S. A., Bassett, A. S., Squires-Wheeler, E.,...Gottesman, I. I. (1997). The New York High-Risk Project: Prevalence and comorbidity of Axis I disorders in offspring of schizophrenic parents at 25 year follow-up. *Archives of General Psychiatry*, 54, 1096-1102.

Ezpeleta, L., Osa, N., Domenech, J. M., Navarro, J. B., Losilla, J. M., & Judez, J. (1997). Diagnostic agreement between clinicians and the Diagnostic Interview for Children and Adolescents-DICA-R-in an outpatient sample. *Journal of Child Psychology and Psychiatry*, 38, 431-440.

Factor, R. J., & Rothblum, E. D. (2007). A study of transgender adults and their non-transgender siblings on demographic characteristics, social support, and experiences of violence. *Journal of Lesbian, Gay, Bisexual and Transgender Research*, 3, 11-30.

Fagot, B. I. (1977). Consequences of moderate cross-gender behaviour in preschool children. *Child Development*, 48, 902-907.

Fagot, B. I. (1985). Changes in thinking about early sex role development. *Developmental Review*, 5, 83-98.

Fagot, B. I., & Leinbach, M. D. (1985). Gender identity: Some thoughts on an old concept. *Journal of the American Academy of Child Psychiatry*, 24, 6894-688.

Fagot, B. I., Leinbach, M. D., & Hagan, R., (1986). Gender labelling and adoption of sex-typed behaviors. *Developmental Psychology*, 22, 440-443.

Farrell, R., & Morrione, T. (1974). Social interaction and stereotypic responses to homosexuals. *Archives of Sexual Behavior*, 3, 425-442.

- Faulkner, A. H., & Cranston, K. (1998). Correlates of same-sex sexual behaviour in a random sample of Massachusetts high school students. *American Journal of Public Health*, 88, 262-266.
- Ferdinand, R. F., & Verhulst, F. C. (1995). Psychopathology from adolescence into young adulthood: an 8-year follow-up study. *American Journal of Psychiatry*, 152, 1586-1594.
- Ferdinand, R. F., Verhulst, F. C., & Wiznitzer, M. (1995). Continuity and change of self-reported problem behaviors from adolescence into young adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry*, 34, 680-690.
- Fergusson, D. M., Horwood, J., & Beautrais, A. L. (1999). Is sexual orientation related to mental health problems and suicidality in young people? *Archives of General Psychiatry*, 56, 876-880.
- Fisk, N. (1973). Gender dysphoria syndrome (the how, why, and what of a disease). In D. Laub & P. Gandy (Eds.), *Proceedings of the second interdisciplinary symposium on gender dysphoria syndrome* (pp. 7-14). Stanford, CA: Stanford University Press.
- Fitzpatrick, K. K., Euton, S. J., Jones, J. N., & Schmidt, N. B. (2005). Gender role, sexual orientation, and suicide risk. *Journal of Affective Disorders*, 87, 35-42.
- Floyd, F. J., & Bakeman, R. (2006). Coming-out across the life-course: Implications of age and historical context. *Archives of Sexual Behavior*, 35, 287-296.
- Fridell, S. R. (2001). *Sex-typed play behaviour and peer relationships of boys with gender identity disorder*. Unpublished doctoral dissertation, University of Toronto, Ontario, Canada.
- Fridell, S. R., Owen-Anderson, A., Johnson, L. L., Bradley, S. J., & Zucker, K. J. (2006). The Playmate and Play Style Preferences Structured Interview: A comparison of

children with gender identity disorder and controls. *Archives of Sexual Behavior*, 35, 729-737.

Fridell, S. R., Zucker, K. J., Bradley, S. J., & Maing, D. M. (1996). Physical attractiveness of girls with gender identity disorder. *Archives of Sexual Behavior*, 25, 17-31.

Frisell, T., Lichtenstein, P., Rahman, Q., & Långström, N. (2010). Psychiatric morbidity associated with same-sex sexual behaviour: influence of minority stress and familial factors. *Psychological Medicine*, 40, 315-324.

Gad, M., & Johnson, J. (1980). Correlates of adolescent life stresses related to race, SES, and levels of perceived support. *Journal of Clinical Child Psychology*, 9, 13-16.

Geller, B., Fox, L. W., & Clark, K. A. (1994). Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 33, 461-468.

Gilman, S. E., Cochran, S. D., Mays, V. M., Hughes, M., Ostrow, D., & Kessler, R. C. (2001). Risk of psychiatric disorders among individuals reporting same-sex sexual partners in the National Comorbidity Survey. *American Journal of Public Health*, 91, 933-939.

Glenn, C. R., & Klonsky, E. D. (2010). A multimethod analysis of impulsivity in nonsuicidal self-injury. *Personality Disorders*, 1, 67-75.

Glenn, N. D., & Weaver, C. N. (1979). Attitudes towards premarital, extramarital, and homosexual relations in the U.S. in the 1970's. *Journal of Sex Research*, 15, 108-118.

Gómez-Gil, E., Trilla, A., Salamero, M., Godás, T., & Valdés, M. (2009). Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Archives of Sexual Behavior*, 38, 378-392.

- Gottschalk, L. (2003). Same-sex sexuality and childhood gender non-conformity: A spurious connection. *Journal of Gender Studies*, 12, 35-50.
- Goy, R. W., Bercovitch, F. B., & McBriar, M. C. (1988). Behavioral masculinisation is independent of genital masculinisation in prenatally androgenised female rhesus macaques. *Hormones and Behavior*, 22, 552-571.
- Green, R. (1970). Sex reassignment: A research strategy. *International Journal of Psychiatry*, 9, 269-273.
- Green, R. (1974). *Sexual identity conflict in children and adults*. New York: Basic Books.
- Green, R. (1976). One-hundred ten feminine and masculine boys: Behavioral contrasts and demographic similarities. *Archives of Sexual Behavior*, 5, 425-446.
- Green, R. (1987). *The "sissy boy syndrome" and the development of homosexuality*. New Haven, CT: Yale University Press.
- Green, R. (2008). Childhood cross-gender behavior and adult homosexuality: Why the link? *Journal of Gay & Lesbian Mental Health*, 12, 17-28.
- Green, R. (2011). The introduction of gender identity disorder of childhood into DSM-III: An historical note. *Journal of Gay & Lesbian Mental Health*, 15, 8-11.
- Green, R., & Money, J. (1960). Incongruous gender role. Nongenital manifestations in prepubertal boys. *Journal of Nervous and Mental Disease*, 131, 160-168.
- Green, R., Roberts, C. W., Williams, K., Goodman, M., & Mixon, A. (1987). Specific cross-gender behavior in boyhood and later homosexual orientation. *British Journal of Psychiatry*, 151, 84-88.
- Grossman, A. H., & D'Augelli, A. R. (2007). Transgender youth and life-threatening behaviors. *Suicide and Life-Threatening Behavior*, 37, 527-537.

- Grossman, A. H., D'Augelli, A. R., & Salter, N. P. (2006). Male-to-female transgender youth: Gender expression milestones, gender atypicality, victimization, and parents' responses. *Journal of GLBT Family Studies*, 2, 71-92.
- Grov, C., Bimbi, D. S., Nanin, J. E., & Parsons, J. T. (2006). Race, ethnicity, gender, and generational factors associated with the coming out process among gay, lesbian, and bisexual individuals. *Journal of Sex Research*, 43, 115-212.
- Haas, A. P., Eliason, M., Mays, V. M., Mathy, R. M., Cochran, S. D., D'Augelli, A. R.,...Clayton, P. J. (2011). Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: Review and recommendations. *Journal of Homosexuality*, 58, 10-51.
- Halpert, S. C. (2002). Suicidal behavior among gay male youth. *Journal of Gay and Lesbian Psychotherapy*, 6, 53-79.
- Haraldsen, I. R., & Dahl, A. A. (2000). Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatrica Scandinavica*, 102, 276-281.
- Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *Journal of Child Psychology and Psychiatry*, 45, 260-273.
- Harry, J. (1985a). Sexual orientation as destiny. *Journal of Homosexuality*, 10, 111-124.
- Harry, J. (1985b). Defeminization and social class. *Archives of Sexual Behavior*, 14, 1-12.
- Heatherington, L., & Lavner, J. A. (2008). Coming to terms with coming out: Review and Recommendations for Family Systems-Focused Research. *Journal of Family Psychology*, 22, 329-343.

- Hellman, R. E., Green, R., Gray, J. L., & Williams, K. (1981). Childhood sexual identity, childhood religiosity, and 'homophobia' as influences in the development of transsexualism, homosexuality, and heterosexuality. *Archives of General Psychiatry*, 38, 910-915.
- Helzer, J. E., Robins, L. N., McEnvoy, L. T., Spitznagel, E. L., Stoltzman, R. K., Farmer, A., & Brockington, I. F. (1985). A comparison of clinical and Diagnostic Interview Schedule diagnoses. *Archives of General Psychiatry*, 42, 657-666.
- Hepp, U., Kraemer, B., Schnyder, U., Miller, N., & Delsignore, A. (2005). Psychiatric comorbidity in gender identity disorder. *Journal of Psychosomatic Research*, 58, 259-261.
- Herek, G. M., & Capitanio, J. P. (1996). "Some of my best friends": Intergroup contact, concealable stigma, and heterosexuals' attitudes toward gay men and lesbians. *Personality and Social Psychology Bulletin*, 22, 412-424.
- Herek, G. M., Cogan, J. C., Gillis, J. R., & Glunt, E. K. (1998). Correlates of internalized homophobia in a community sample of lesbians and gay men. *Journal of the Gay and Lesbian Medical Association*, 2, 17-25.
- Herek, G. M., Gillis, J. R., Cogan, J. C., & Glunt, E. K. (1997). Hate crime victimization among lesbian, gay and bisexual youth. *Journal of Interpersonal Violence*, 12, 195-215.
- Herek, G. M., & Glunt, E. K. (1993). Interpersonal contact and heterosexuals' attitudes toward gay men: Results from a national survey. *Journal of Sex Research*, 30, 239-244.
- Herjanic, B., & Reich, W. (1982). Development of a structured psychiatric interview for children: Agreement between child and parent on individual symptoms. *Journal of Abnormal Child Psychology*, 10, 307-324.

- Herjanic, B., & Reich, W. (1983). *Diagnostic Interview for Children and Adolescents (DICA-C): Child version*. St. Louis, MO: Washington University School of Medicine.
- Hershberger, S. L. (1997). A twin registry study of male and female sexual orientation. *Science*, 261, 321-327.
- Hesselbrock, V., Stabenau, J., Hesselbrock, M., Mirkin, P., & Meyer, R. (1982). A comparison of two interview schedules: The Schedule for Affective Disorders and Schizophrenia-Lifetime and the National Institute of Mental Health Diagnostic Interview Schedule. *Archives of General Psychiatry*, 39, 674-677.
- Hill, S. A. (2002). Teaching and doing gender in African American families. *Sex Roles*, 47, 493-506.
- Hill, D. B., Rozanski, C., Carfagnini, J., & Willoughby, B. (2005). Gender identity disorders in childhood and adolescence: A critical inquiry. *Journal of Psychology & Human Sexuality*, 17, 7-34.
- Hines, M. (2002). Sexual differentiation of human brain and behaviour. In D. W. Plaff, A. P. Arnold, A. M. Etgen, S. E. Fahrbach, & R. T. Rubin (Eds.), *Hormones, brain, and behaviour* (Vol. 4, pp. 425-262). San Diego, CA: Academic Press.
- Hines, M. (2010). Gendered behavior across the lifespan. In R. M. Lerner (Ed.), *The handbook of life-span development* (Vol. 2, pp. 341-378). New York: Wiley.
- Hines, M. (2011). Gender development and the human brain. *Annual Review of Neuroscience*, 34, 69-88.
- Hines, M., Brook, C., & Conway, G. S. (2004). Androgen and psychosexual development: core gender identity, sexual orientation and recalled childhood gender role behavior in

women and men with congenital adrenal hyperplasia (CAH). *Journal of Sex Research*, 41, 75-81.

Hoening, J., Kenna, J., & Youd, A. (1970). Social and economic aspects of transsexualism. *British Journal of Psychiatry*, 117, 163-172.

Hofstra, M. B., van der Ende, J., & Verhulst, F. C. (2000). Continuity and change of psychopathology from childhood into adulthood: A 14-year follow-up study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 39, 850-858.

Hofstra, M. B., van der Ende, J., & Verhulst, F. C. (2001). Child and adolescent problems predict DSM-IV disorders in adulthood: A 14-year follow-up of a Dutch Epidemiological Sample. *Journal of the American Academy of Child & Adolescent Psychiatry*, 341, 182-189.

Holden, R. R., & Fekken, G. C. (1989). Three common social desirability scales: Friends, acquaintances, or strangers? *Journal of Research in Personality*, 23, 180-191.

Hollingshead, A. B. (1975). *Four factor index of social status*. (Unpublished manuscript). Department of Sociology, Yale University, New Haven, CT.

Hollingshead, A. B., & Redlich, F. C. (1958). *Social class and mental illness*. New York: Wiley.

Horton, J., Compton, W. M., & Cottler, L. B. (1998). Assessing psychiatric disorders among drug users: reliability of the revised DIS-IV (abstract). In L. Harris (Ed.), *NIDA research monograph: Problems of drug dependence* (p. 205). Washington, DC: NIH.

Hoshiai, M., Matsumoto, Y., Sato, T., Ohnishi, M., Okabe, N., Kishimoto, Y.,...Kurodo, S. (2010). Psychiatric comorbidity among patients with gender identity disorder. *Psychiatry and Clinical Neurosciences*, 64, 514-519.

- Hoult, T. (1983/1984). Human sexuality in biological perspective. *Journal of Homosexuality*, 9, 137-156.
- Hudson, C. G. (1988). Socioeconomic status and mental illness: Implications of the research for policy and practice. *Journal of Sociology and Social Welfare*, 15, 27-54.
- Hudson, C. G. (2005). Socioeconomic status and mental illness: Tests of the social causation and selection hypotheses. *American Journal of Orthopsychiatry*, 75, 3-18.
- Irwin, P., & Thompson, N. L. (1977). Acceptance of the rights of homosexuals: A social profile. *Journal of Homosexuality*, 3, 107-121.
- Isay, R. A. (1997, November 21). Remove gender identity disorder in DSM. *Psychiatric News*, 32(22), 9-13.
- Jacobson, C. M., & Gould, M. (2007). The epidemiology and phenomenology of non-suicidal self-injurious behavior among adolescents: A critical review of the literature. *Archives of Suicide Research*, 11, 127-147.
- Jenkins, J. (2008). Psychosocial adversity and resilience. In M. Rutter, D. V. M. Bishop, D. S. Pine, S. Scott, J. Stevenson, E. Taylor, & A. Thapar (Eds.), *Rutter's child and adolescent psychiatry* (pp. 377-391). Oxford: Blackwell Publishing.
- Jensen, L., Gambles, D., & Olsen, J. (1988). Attitudes towards homosexuality: A cross-cultural analysis of predictors. *The International Journal of Social Psychiatry*, 34, 47-57.
- Johnson, L. L., Bradley, S. J., Birkenfeld-Adams, A. S., Kuksis, M. A. R., Maing, D. M., Mitchell, J. N., et al. (2004). A parent-report Gender Identity Questionnaire for Children. *Archives of Sexual Behavior*, 33, 105-116.

- Jolles, I. (1952). A study of validity of some hypotheses for the qualitative interpretation of the H-T-P for children of elementary school age: I. Sexual identification. *Journal of Clinical Psychology*, 8, 113-118.
- Kallman, F. J. (1952). Twin and sibship study of overt male homosexuality. *American Journal of Human Genetics*, 4, 136-146.
- Kessler, R. C., Borges, G., & Walters, E. E. (1999). Prevalence and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Archives of General Psychiatry*, 56, 617-626.
- Kessler, S. J., & McKenna, W. (1978). *Gender: An ethnomethodological approach*. Chicago: University of Chicago Press.
- Kilpatrick, D. G., Saunders, B. E., & Smith, D. W. (2002). *Research in brief: Youth victimization: Prevalence and implications*. Washington, DC: U.S. Department of Justice, National Institute of Justice.
- King, M. F., & Brunner, G. C. (2000). Social desirability bias: A neglected aspect of validity testing. *Psychology and Marketing*, 17, 79-103.
- King, M., Semlyen, J., Tai, S. S., Killaspy, H., Osborn, D., Popelyuk, D., et al. (2008). A systematic review of mental disorder, suicide, and deliberate self-harm in lesbian, gay and bisexual people. *BMC Psychiatry*, 8. doi:10.1186/1471-244X-8-70.
- Kinsey, A. C., Pomeroy, W. B., & Martin, C. E. (1948). *Sexual behavior in the human male*. Philadelphia: W. B. Saunders.
- Kirk, K. M., Bailey, J. M., Dunne, M. P., & Martin, N. G. (2000). Measurement models for sexual orientation in a community twin sample. *Behavior Genetics*, 30, 345-356.

- Klin, A., Danovitch, J. H., Merz, A. B., & Volkmar, F. R. (2007). Circumscribed interests in higher functioning individuals with autism spectrum disorders: An exploratory study. *Research & Practice for Persons with Severe Disabilities*, 32, 89-100.
- Kosky, R. J. (1987). Gender-disordered children: Does inpatient treatment help? *Medical Journal of Australia*, 146, 565-569.
- Kulkin, H. S., Chauvin, E. A., & Percle, G. A. (2000). Suicide among gay and lesbian adolescents and young adults. A review of the literature. *Journal of Homosexuality*, 40, 1-29.
- Lambert, S. L. (2009). *The assessment of body image in boys with gender identity disorder: A comparison to clinical control boys and community control boys*. Unpublished doctoral dissertation, York University, Toronto, Ontario, Canada.
- Landén, M., & Rasmussen, P. (1997). Gender identity disorder in a girl with autism: A case report. *European Child & Adolescent Psychiatry*, 6, 170-173.
- Landolt, M. A., Bartholomew, K., Saffrey, C., Oram, D., & Perlman, D. (2004). Gender nonconformity, childhood rejection, and adult attachment: A study of gay men. *Archives of Sexual Behavior*, 33, 117-128.
- Langer, S. J., & Martin, J. I. (2004). How dresses can make you mentally ill: Examining gender identity disorder in children. *Child and Adolescent Social Work Journal*, 21, 5-23.
- Langevin, R. (1985). *Sexual strands: Understanding and treating sexual anomalies in men*. Hillsdale, NJ: Erlbaum.

- Långström, N., Rahman, Q., Carlström, E., & Lichtenstein, P. (2010). Genetic and environmental effects on same-sex sexual behavior: A population based study of twin in Sweden. *Archives of Sexual Behavior*, 39, 75-80.
- Laumann, E. O., Gagnon, J. H., Michael, R. T., & Michaels, S. (1994). *The social organization of sexuality: Sexual practices in the United States*. Chicago: University of Chicago Press.
- Lawrence, A., & Zucker, K. J. (2012). Gender identity disorders. In D. C. Biedel & M. Hersen (Eds.), *Adult psychopathology and diagnosis* (6th ed., pp. 601-636). Hoboken, NJ: John Wiley & Sons.
- Lebovitz, P. S. (1972). Feminine behavior in boys: Aspects of its outcome. *American Journal of Psychiatry*, 128, 1283-1289.
- Lemelle, A. J., & Battle, J. (2004). Black masculinity matters in attitudes toward gay males. *Journal of Homosexuality*, 47, 39-41.
- LeVay, S. (1993). *The sexual brain*. Massachusetts: MIT Press.
- LeVay, S. (2011). *Gay, straight, and the reason why: The science of sexual orientation*. New York: Oxford University Press.
- Lever, J. (1994, August 23). Sexual revelations: The 1994 Advocate survey of sexuality and relationships: The mean. *The Advocate*, 18-24.
- Liu, R. T., & Mustanski, B. (2012). Suicidal ideation and self-harm in lesbian, gay, bisexual, and transgender youth. *American Journal of Preventative Medicine*, 42, 221-228.
- Lippa, R. (1998). Gender-related individual differences and the structure of vocational interests: The importance of people-things dimension. *Journal of Personality and Social Psychology*, 74, 996-1009.

- Lippa, R. A. (2005). *Gender, nature, and nurture* (2nd ed.). Mahwah, NJ: Lawrence Erlbaum Associates.
- Lombardi, E. L., Wilchins, R. A., Priesing, D., & Malfouf, D. (2001). Gender violence: Transgender experiences with violence and discrimination. *Journal of Homosexuality*, 42, 89-101.
- Lottes, I. L., & Kuriloff, P. J. (1994). The impact of college experience on political and social attitudes. *Sex Roles*, 31, 31-54.
- Maccoby, E. E. (1998). *The two sexes: Growing up apart, coming together*. Cambridge, MA: Belknap Press.
- MacDonald, A. P. (1983). A little bit of lavender goes a long way: A critique of research on sexual orientation. *Journal of Sex Research*, 19, 94-100.
- MacFarlane, D. F. (1984). Transsexual prostitution in New Zealand: Predominance of persons of Maori extraction. *Archives of Sexual Behavior*, 13, 301-309.
- Maguen, S., & Shipherd, J. C. (2010). Suicide risk among transgender individuals. *Psychology & Sexuality*, 1, 34-43.
- Martin, C. L. (1989). Children's use of gender-related information in making social judgements. *Developmental Psychology*, 25, 80-88.
- Martin, H. P. (1991). The coming-out process for homosexuals. *Hospital and Community Psychiatry*, 42, 158-162.
- Masi, G., Mucci, M., & Millepiedi, S. (2001). Separation anxiety disorder in children and adolescents. *CNS Drugs*, 15, 93-104.

- Mathijssen, J. J. J. P., Koot, H. M., & Verhulst, F. C. (1999). Predicting change in problem behavior from child and family characteristics and stress in referred children and adolescents. *Development and Psychopathology*, *11*, 305-320.
- Mathy, R. M. (2003). Transgender identity and suicidality in a nonclinical sample: Sexual orientation, psychiatric history, and compulsive behaviors. *Journal of Psychology & Human Sexuality*, *14*, 47-65.
- Maughan, B., & Rutter, M. (2008). Development and psychopathology: A life course perspective. In M. Rutter, D. V. M. Bishop, D. S. Pine, S. Scott, J. Stenvenson, E. Taylor, & A. Thapar (Eds.), *Rutter's child and adolescent psychiatry* (pp. 160-181). Oxford: Blackwell Publishing.
- Mays, V. M., & Cochran, S. D. (2001). Mental health correlates of perceived discrimination among lesbian, gay, and bisexual adults in the United States. *American Journal of Public Health*, *91*, 1869-1876.
- McDaniel, J. S., Purcell, D. W., & D'Augelli, A. R. (2001). The relationship between sexual orientation and risk for suicide: Research findings and future direction for research and prevention. *Suicide and Life-Threatening Behavior*, *31*(Suppl.), 60-83.
- McDonald, G. J. (1982). Individual differences in the coming out process for gay men: implications for theoretical models. *Journal of Homosexuality*, *8*, 47-60.
- McLanahan, S., & Sandefur, G. (1994). *Growing up with a single parent: What hurts, what helps*. Cambridge: Harvard University Press.
- McNeil, T. F., & Kaij, L. (1979). Etiological relevance of comparisons of high-risk and low-risk group. *Acta Psychiatrica Scandinavica*, *59*, 545-560.

- Menvielle, E. J. (1998). Gender identity disorder [Letter to the Editor]. *Journal of the American Academy of Child and Adolescent Psychiatry*, 37, 243-244.
- Menvielle, E. J. (2012). A comprehensive program for children with gender variant behaviors and gender identity disorders. *Journal of Homosexuality*, 59, 357-369.
- Menvielle, E. J., & Hill, D. B. (2011). An affirmative intervention for families with gender-variant children: A process evaluation. *Journal of Gay & Lesbian Mental Health*, 15, 94-123.
- Menvielle, E. J., & Tuerk, C. (2002). A support group for parents of gender-nonconforming boys. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41, 1010-1013.
- Meyer, I. H. (1995). Minority stress and mental health in gay men. *Journal of Health and Social Behavior*, 36, 38-56.
- Meyer, I. H. (2003). Prejudice, social stress, and mental health in lesbian, gay and bisexual populations: Conceptual issues and research evidence. *Psychological Bulletin*, 129, 647-697.
- Meyer, W. I., Bockting, W. O., Cohen-Kettenis, P., Coleman, E., DiCeglie, D., Devor, H., et al. (2001). The Harry Benjamin International Gender Dysphoria Associations's Standards of Care for Gender Identity Disorders, sixth version. *Journal of Psychology and Human Sexuality*, 13, 1-30.
- Meyer-Bahlburg, H. F. L. (1985). Gender identity disorder of childhood: Introduction. *Journal of the American Academy of Child Psychiatry*, 24, 681-683.
- Meyer-Bahlburg, H. F. L. (2002). Gender identity disorder in young boys: A parent-and peer based treatment protocol. *Clinical Child Psychology and Psychiatry*, 7, 360-376.

Meyer-Bahlburg, H. F. L. (2010). From mental disorder to iatrogenic hypogonadism:

Dilemmas in conceptualizing gender identity variants as psychiatric conditions. *Archives of Sexual Behavior*, 39, 461-476.

Meyer-Bahlburg, H. F. L., Dolezal, C., Baker, S. W., Ehrhardt, A. A., & New, M. I. (2006).

Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. *Archives of Sexual Behavior*, 35, 667-684.

Meyer-Bahlburg, H. F. L., Dolezal, C., Baker, S. W., & New, M. I. (2008). Sexual

orientation in women with classical or non-classical congenital adrenal hyperplasia as a function of degree of prenatal androgen excess. *Archives of Sexual Behavior*, 37, 85-99.

Michael, R., Gagnon, J., Laumann, E., & Kolata, G. (1994). *Sex in America: A definitive survey*. Boston: Little, Brown.

Minter, S. (1999). Diagnosis and treatment of gender identity disorder in children. In M.

Rottnek (Ed.), *Sissies and tomboys. Gender nonconformity and homosexual childhood* (pp. 9–33). New York: New York University Press.

Money, J. (1955). Hermaphroditism, gender and precocity in hyperadrenocorticism:

Psychologic findings. *Bulletin of the Johns Hopkins Hospital*, 96, 253-264.

Money, J. (1988). *Gay, straight, and in-between: The sexology of erotic orientation*. New

York: Oxford University Press.

Money, J. (1994). The concept of gender identity disorder in childhood and adolescence after

39 years. *Journal of Sex & Marital Therapy*, 20, 163-177.

Money, J., & Russo, A. J. (1979). Homosexual outcome of discordant gender identity/role in childhood: Longitudinal follow-up. *Journal of Pediatric Psychology*, 4, 29-41.

- Morrow, D. F. (2004). Social work practice with gay, lesbian, bisexual, and transgender adolescents. *Families in Society*, 85, 91-99.
- Muehlenhard, C. L., & Peterson, Z. D. (2011). Distinguishing between *sex* and *gender*: History, current conceptualizations, and implications. *Sex Roles*, 64, 791-803.
- Mukkades, N. M. (2002). Gender identity problems in autistic children. *Child: Care, Health & Development*, 28, 529-532.
- Mustanski, B. S., Chivers, M. L., & Bailey, J. M. (2002). A critical review of recent biological research on human sexual orientation. *Annual Review of Sex Research*, 13, 89-140.
- Neale, J. M., & Weintraub, S. (1975). Children vulnerable to psychopathology: The Stony Brook High-Risk Project. *Journal of Abnormal Child Psychology*, 3, 95-113.
- Nemoto, T., Bödeker, B., & Iwamoto, M. (2011). Social support, exposure to violence and transphobia, and correlates of depression among male-to-female transgender women with a history of sex work. *American Journal of Public Health*, 101, 1980-1988.
- Newman, B. S., & Muzzonigro, P. G. (1993). The effects of traditional family values on the coming out process of gay male adolescents. *Adolescence*, 28, 213-226.
- Newton-Howes, G., Tryer, P., Anagnostakis, K., Cooper, S., Bowden-Jones, O., Weaver, T., & COSMIC Study Team. (2010). The prevalence of personality disorder, its comorbidity with mental state disorders, and its clinical significance in community mental health teams. *Social Psychiatry and Psychiatric Epidemiology*, 45, 453-460.
- Nordenström, A., Servin, A., Bohlin, G., Larsson, A., & Wedell, A. (2002). Sex-typed toy play behavior correlates with the degree of prenatal androgen exposure assessed by

CYP21 genotype in girls with congenital adrenal hyperplasia. *The Journal of Clinical Endocrinology and Metabolism*, 87, 5119-5124.

Nuttbrock, L., Hwahng, S., Bockting, W., Rosenblum, A., Mason, M., Macri, M., & Becker, J. (2010). Psychiatric impact of gender-related abuse across the life course of male-to-female transgender persons. *Journal of Sex Research*, 47, 12-23.

Nyberg, K. L., & Alston, J. P. (1976). Analysis of public attitudes towards homosexuality. *Journal of Homosexuality*, 2, 99-107.

Oswalt, S. B., & Wyatt, T. J. (2011). Sexual orientation and differences in mental health, stress, and academic performance in a national sample of US college students. *Journal of Homosexuality*, 58, 1255-1280.

Parker, J. G., Rubin, K. H., Price, J. M., & DeRosier, M. E. (1995). Peer relationships, child development and adjustment: A developmental psychopathological perspective. In D. Cicchetti & D. Cohen (Eds.), *Developmental psychopathology: Vol 2. Risk, disorder, and adaptation* (pp. 96-161). New York: Wiley.

Pasterski, V. L., Geffner, M. E., Brain C., Hindmarsh, P., Brook, C., & Hines, M. (2005). Prenatal hormones and postnatal socialization by parents as determinants of male-typical toy play in girls with congenital adrenal hyperplasia. *Child Development*, 76, 264-278.

Pasterski, V. L., Geffner, M. E., Brain C., Hindmarsh, P., Brook, C., & Hines, M. (2011). Prenatal hormones and childhood sex segregation: Playmate and play style preferences in girls with congenital adrenal hyperplasia. *Hormones and Behavior*, 59, 549-555.

Pasterski, V. L., Hindmarsh, P., Geffner, M. E., Brook, C., Brain C., & Hines, M. (2007). Increased aggression and activity level in 3- to 11-year-old girls with congenital adrenal hyperplasia. *Hormones and Behavior*, 52, 368-374.

- Patterson, C. J., Vaden, N. A., Griesler, P. C., & Kupersmidt, J. B. (1991). Income level, gender, ethnicity, and household composition as predictors of children's peer companionship outside of school. *Journal of Applied Developmental Psychology, 12*, 447-465.
- Paul, J. P. (1993). Childhood cross-gender behavior and adult homosexuality: The resurgence of biological models of sexuality. *Journal of Homosexuality, 24*, 41-54.
- Pickstone-Taylor, S. D. (2003). Children with gender nonconformity [Letter to the Editor]. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*, 266.
- Pillard, R. C., Poumadere, J., & Carretta, R. A. (1981). Is homosexuality familial? A review, some data, and a suggestion. *Archives of Sexual Behavior, 10*, 465-475.
- Pillard, R. C., & Weinrich, J. D. (1986). Evidence of familial nature of male homosexuality. *Archives of General Psychiatry, 43*, 808-812.
- Plöderl, M., & Fartacek, R. (2009). Childhood gender nonconformity and harassment as predictors of suicidality among gay, lesbian, bisexual, and heterosexual Austrians. *Archives of Sexual Behavior, 38*, 400-410.
- Postema, L., Wood, H., Singh, D., Fantus, S., Hyun, J., Leef, J., Bradley, S. J., & Zucker, K. J. (2011). *Brief report: Do children with gender identity disorder have intense/obsessional interests? A preliminary study.* Manuscript submitted for publication.
- Rekers, G. A., Bentler, P. M., Rosen, A. C., & Lovaas, O. I. (1977). Child gender disturbances: A clinical rationale for intervention. *Psychotherapy: Theory, Research and Practice, 14*, 2-11.
- Rekers, G. A., & Lovaas, I. (1974). Behavioral treatment of deviant sex role behaviors in a male child. *Journal of Applied Behavior Analysis, 7*, 173-190.

- Rekers, G. A., & Yates, C. E. (1976). Sex-typed play in feminoid boys vs. normal boys and girls. *Journal of Abnormal Child Psychology*, 4, 1-8.
- Remafedi, G., French, S., Story, M., Resnick, M. D., & Blum, R. (1998). The relationship between suicide risk and sexual orientation: Results of a population-based study. *American Journal of Public Health*, 88, 57-60.
- Richardson, J. (1996). Setting limits of gender health. *Harvard Review of Psychiatry*, 4, 49-53.
- Richardson, J. (1999). Response: Finding the disorder in gender identity disorder. *Harvard Review of Psychiatry*, 7, 43-50.
- Rieger, G., Chivers, M. L., & Bailey, J. M. (2005). Sexual arousal patterns of bisexual men. *Psychological Science*, 16, 579-584.
- Rieger G., Linsenmeier, J. A., Gygax, L., & Bailey, J. M. (2008). Sexual orientation and childhood gender nonconformity: Evidence from home videos. *Developmental Psychology*, 44, 46-58.
- Rieger G., Linsenmeier, J. A., Gygax, L., Garcia, S., & Bailey, J. M. (2010). Dissecting “gaydar”: accuracy and the role of masculinity-femininity. *Archives of Sexual Behavior*, 39, 124-140.
- Rieger, G., & Savin-Williams, R. (2012). Gender nonconformity, sexual orientation, and psychological well-being. *Archives of Sexual Behavior*, 41, 611-621.
- Robins, L. N. (1966). *Deviant children grown up: A sociological and psychiatric study of sociopathic personality*. Baltimore: Williams and Wilkins.
- Robins, L. N., Cottler, L. B., Bucholz, K. K., & Compton, W. (1995). *Diagnostic Interview Schedule, Version 4*. St. Louis, MO: Washington University.

Robins, L. N., & Helzer, J. (1985). *The Diagnostic Interview Schedule Version III-A*. St. Louis, MO: Washington University.

Robins, L. N., Helzer, J. E., Croughan, J., & Ratcliff, K. S. (1981). National Institute of Mental Health Diagnostic Interview Schedule: Its history, characteristics, and validity. *Archives of General Psychiatry*, 38, 381-389.

Rogers, R. (2001). *Handbook of diagnostic and structured interviewing*. New York: Guilford Press.

Romano, E., Bell, T., & Billette, J-M. (2011). Prevalence and correlates of multiple victimization in a nation-wide adolescent sample. *Child Abuse & Neglect*, 35, 468-479.

Rosario, M., Schrimshaw, E. W., & Hunter, J. (2008). Predicting different patterns of sexual identity development overtime among lesbian, gay, and bisexual youths: A cluster analytic approach. *American Journal of Community Psychology*, 42, 266-282.

Rosario, M., Schrimshaw, E. W., Hunter, J., & Braun, L. (2006). Sexual identity development among lesbian, gay, and bisexual youths: Consistency and change over time. *Journal of Sex Research*, 43, 46-58.

Rosin, H. (2008, November). A boy's life. *The Atlantic*, 302, 56-71.

Ross, M. W.(1983). *The married homosexual man: A psychological study*. Boston: Routledge & Kegan Paul.

Ruble, D. N., Martin, C. L., & Berenbaum, S. A. (2006). Gender development. In W. Damon & R. M. Lerner (Series eds.) and N. Eisenberg (Vol. ed.), *Handbook of child psychology: Vol. 3. Social, emotional, and personality development* (6th ed., pp. 858-932). New York: Wiley.

- Ryan, C., Huebner, D., Diaz, R. M., & Sanchez, J. (2009). Family rejection as a predictor of negative health outcomes in white and Latino lesbian, gay, and bisexual young adults. *Pediatrics, 123*, 346-352.
- Saeger, K. (2006). Finding our way: Guiding a young transgender child. *Journal of GLBT Family Studies, 2*, 207-245.
- Safren, S. A., & Heimberg, R. G. (1999). Depression, hopelessness, suicidality, and related factors in sexual minority and heterosexual adolescents. *Journal of Consulting and Clinical Psychology, 67*, 859-866.
- Sandfort, T. G. M., Bakker, F., Schellevis, F. G., & Vanwesenbeeck, I. (2006). Sexual orientation and mental and physical health status: Findings from a Dutch population survey. *American Journal of Public Health, 96*, 1119-1125.
- Sattler, J. M. (2001). *Assessment of children: Cognitive applications* (4th ed.). San Diego: Jerome M. Sattler Publisher, Inc.
- Saunders, B. E. (2003). Understanding children exposed to violence: Toward an integration of overlapping fields. *Journal of Interpersonal Violence, 18*, 356-376.
- Savin-Williams, R. C. (1998). The disclosure to families of same-sex attractions by lesbian, gay, and bisexual youths. *Journal of Research on Adolescence, 8*, 49-68.
- Savin-Williams, R. C., & Diamond, L. M. (2000). Sexual identity trajectories among sexual-minority youths: Gender comparisons. *Archives of Sexual Behavior, 29*, 607-627.
- Savin-Williams, R. C., & Dube, E. M. (1998). Parental reactions to their child's disclosure of a gay/lesbian identity. *Family Relations, 47*, 7-13.
- Savin-Williams, R. C., & Ream, G. L. (2003). Suicide attempts among sexual-minority male youth. *Journal of Clinical Child and Adolescent Psychology, 32*, 509-522.

- Schneider, B. H. (2000). *Friends and enemies: Peer relations in childhood*. London, England: Arnold.
- Schwartz, G., Kim, R. M., Kolundzija, A. B., Rieger, G., & Sanders, A. R. (2010). Biodemographic and physical correlates of sexual orientation in men. *Archives of Sexual Behavior*, 39, 93-109.
- Sedgwick, E. K. (1991). How to bring your kids up gay. *Social Text*, 9, 18-27.
- Sell, R. L. (1997). Defining and measuring sexual orientation: A review. *Archives of Sexual Behavior*, 26, 643-658.
- Servin, A., Nordenström, A., Larsson, A., & Bohlin, G. (2003). Prenatal androgens and gender-typed behavior: a study of girls with mild and severe forms of congenital adrenal hyperplasia. *Developmental Psychology*, 39, 440-450.
- Shaffer, N. (2005). Transgender patients: Implications for emergency department policy and practice. *Journal of Emergency Nursing*, 31, 405-407.
- Silverthorn, N. A., & Gekoski, W. L. (1995). Social desirability effects on measures of adjustment to university, independence from parents, and self-efficacy. *Journal of Clinical Psychology*, 51, 244-251.
- Simon, L., Zsolt, U., Fogd, D., & Czobor, P. (2011). Dysfunctional core beliefs, perceived parenting behavior and psychopathology in gender identity disorder: A comparison of male-to-female, female-to-male transsexual and nontranssexual control subjects. *Journal of Behavior Therapy and Experimental Psychiatry*, 42, 38-45.
- Singh, D., Deogracias, J. J., Johnson, L. L., Bradley, S. J., Kibblewhite, S. J., Meyer-Bahlburg, H. F. L., et al. (2010). The gender identity/gender dysphoria questionnaire for adolescents and adults: Further validity evidence. *Journal of Sex Research*, 47, 49-58.

- Singh, D., McMain, S., & Zucker, K. J. (2011). Gender identity and sexual orientation in women with Borderline Personality Disorder. *Journal of Sexual Medicine*, 8, 447-454.
- Smith, Y. L. S., van Goozen, S. H. M., & Cohen-Kettenis, P. T. (2001). Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: A prospective follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40, 472-481.
- Smith, Y. L. S., van Goozen, S. H. M., Kuiper, A. J., & Cohen-Kettenis, P. T. (2005). Transsexual subtypes: clinical and theoretical significance. *Psychiatry Research*, 137, 151-160.
- Spiegel, A. (2008, May). Parents consider treatment to delay son's puberty: New therapy would buy time to resolve gender crisis. *NPR, All Things Considered*. Retrieved June 13, 2011 from www.npr.org.
- Steensma, T. D., Biemond, R., de Boer, F., & Cohen-Kettenis, P. T. (2011). Desisting and persisting gender dysphoria after childhood: A qualitative follow-up study. *Clinical Child Psychology and Psychiatry*, 16, 499-516.
- Steensma, T. D., & Cohen-Kettenis, P. T. (2011). Gender transitioning before puberty? [Letter to the Editor]. *Archives of Sexual Behavior*, 40, 649-650.
- Steensma, T. D., van der Ende, J., Verhulst, F. C., & Cohen-Kettenis, P. T. (2012). Gender variance in childhood and sexual orientation in adulthood: A prospective study. *Journal of Sexual Medicine*. Advance online publication. doi: 10.1111/j.1743-6109.2012.02701.x

- Stein, E. (2012). Commentary on the treatment of gender-variant and gender-dysphoric children and adolescents: Common themes and ethical reflections. *Journal of Homosexuality*, 59, 480-500.
- Stieglitz, K. A. (2010). Development, risk, and resilience of transgender youth. *Journal of the Association of Nurses in Aids Care*, 21, 192-206.
- Stokes, J. P., Damon, W., & McKirnan, D. J. (1997). Predictors of movement towards homosexuality: A longitudinal study of bisexual men. *Journal of Sex Research*, 34, 304-312.
- Stoller, R. J. (1964). The hermaphroditic identity of hermaphrodites. *Journal of Nervous and Mental Disease*, 139, 453-457.
- Storms, M. D. (1980). Theories of sexual orientation. *Journal of Personality and Social Psychology*, 38, 783-792.
- Strahan, R., & Gerbasi, K. C. (1972). Short, homogeneous versions of Marlowe-Crowne Social Desirability Scale. *Journal of Clinical Psychology*, 28, 191-193.
- Szatmari, P., Bryson, S. E., Boyle, M. H., Streiner, D. L., & Duku, E. (2003). Predictors of outcome among high functioning children with autism and Asperger's Syndrome. *Journal of Child Psychology and Psychiatry*, 44, 520-528.
- Tan, L., & Grace, R. C. (2008). Social desirability and sexual offenders: A review. *Sexual Abuse: A Journal of Research and Treatment*, 20, 61-87.
- Taywaditep, K. J. (2001). Marginalization among the marginalized: Gay men's anti-effeminacy attitudes. *Journal of Homosexuality*, 42(1), 1-28.

- Toomey, R. B., Ryan, C., Diaz, R. M., Card, N. A., & Russell, S. T. (2010). Gender non-conforming lesbian, gay, bisexual, and transgender youth: School victimization and young adult psychological adjustment. *Developmental Psychology, 46*, 1580-1589.
- van Beijsterveldt, C. E. M., Hudziak, J. J., & Boomsma, D. I. (2006). Genetic and environmental influences on cross-gender behavior and relation to behavior problems: A study of Dutch twins at ages 7 and 10 years. *Archives of Sexual Behavior, 35*, 647-658.
- Vanderburgh, R. (2009). Appropriate therapeutic care for families with pre-pubescent transgender/gender-dissonant children. *Child and Adolescent Social Work Journal, 26*, 135-154.
- VanderLaan, D. P., Gothreau, L. M., Bartlett, N. H., & Vasey, P. L. (2011a). Separation anxiety in feminine boys: Pathological or prosocial? *Journal of Gay & Lesbian Mental Health, 15*, 30-45.
- VanderLaan, D. P., Gothreau, L. M., Bartlett, N. H., & Vasey, P. L. (2011b). Recalled separation anxiety and gender-atypicality in childhood: A study of Canadian heterosexual and homosexual men and women. *Archives of Sexual Behavior, 40*, 1233-1240.
- van Kesteren, P. J. M., Asscheman, H., Megens, J. A. J., & Gooren, L. J. G. (1997). Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clinical Endocrinology, 47*, 337-342.
- Vasey, P. L., & Bartlett, N. H. (2007) What can the Samoan “fa’afafine” teach us about the Western concept of gender identity disorder in childhood. *Perspectives in Biology and Medicine, 50*, 481-490.

- Vasey, P. L., VanderLaan, D. P., Gothreau, L. G., & Bartlett, N. H. (2011). Traits of separation anxiety in childhood: A retrospective study in Samoan men, women, and fa'afafine. *Archives of Sexual Behavior*, 40, 511-517.
- Verhulst, F. C. (1995). The epidemiology of child and adolescent psychopathology: Strengths and limitations. In F. C. Verhulst & H. M. Koot (Eds.), *The epidemiology of child and adolescent psychopathology* (pp. 1-21). New York: Oxford.
- Verhulst, F. C., & Koot, H. M. (1991). Longitudinal research in child and adolescent psychiatry. *Journal of the American Academy of Child and Adolescent Psychiatry*, 30, 361-368.
- Verschoor, A. M., & Poortinga, J. (1988). Psychosocial differences between Dutch male and female transsexuals. *Archives of Sexual Behavior*, 17, 173-178.
- Vilain, E. (2000). Genetics of sexual development. *Annual Review of Sex Research*, 11, 1-25.
- Wallien, M. S. C., & Cohen-Kettenis, P. T. (2008). Psychosexual outcome of gender dysphoric children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 47, 1413-1423.
- Wallien, M. S. C., Quilty, L. C., Steensma, T. D., Singh, D., Lambert, S. L., Leroux, A.,...Zucker, K. J. (2009). Cross-national replication of the Gender Identity Interview for Children. *Journal of Personality Assessment*, 91, 545-552.
- Wallien, M. S. C., Swaab, H., & Cohen-Kettenis, P. T. (2007). Psychiatric comorbidity among children with gender identity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46, 1307-1314.

- Wallien, M. S. C., van Goozen, S. H. M., & Cohen-Kettenis, P. T. (2007). Physiological correlates of anxiety in children with gender identity disorder. *European Child & Adolescent Psychiatry, 16*, 309-315.
- Wallien, M. S. C., Veenstra, R., Kreukels, B. P. C., & Cohen-Kettenis, P. T. (2010). Peer group status of gender dysphoric children: A sociometric study. *Archives of Sexual Behavior, 39*, 553-560.
- Wechsler, D. (1974). *Manual: Wechsler Intelligence Scale for Children--Revised*. New York: Psychological Corporation.
- Wechsler, D. (1981). *Wechsler Adult Intelligence Scale--Revised*. San Antonio, TX: The Psychological Corporation.
- Wechsler, D. (1991). *Wechsler Intelligence Scale for Children--Third Edition*. San Antonio, TX: The Psychological Corporation.
- Wechsler, D. (1997). *Wechsler Adult Intelligence Scale--Third Edition*. San Antonio, TX: The Psychological Corporation.
- Wechsler, D. (2002). *Wechsler Preschool and Primary Scale of Intelligence--Third Edition*. San Antonio, TX: Psychological Corporation.
- Wechsler, D. (2003). *Wechsler Intelligence Scale for Children--Fourth Edition*. San Antonio, TX: The Psychological Corporation.
- Wechsler, D. (2008). *Wechsler Adult Intelligence Scale--Fourth Edition*. San Antonio, TX: The Psychological Corporation.
- Weissman, M. M., Bland, R. C., Canino, G. J., Greenwald, S., Hwu, H. G., Joyce, P. R.,...Yeh, E. K. (1999). Prevalence of suicide ideation and suicide attempts in nine countries. *Psychological Medicine, 29*, 9-17.

- Weitz, C., & Osburg, S. (1996). Transsexualism in Germany: Empirical data on epidemiology and application of the German Transsexuals' act during its first 10 years. *Archives of Sexual Behavior*, 25, 409-425.
- Welner, Z., Reich, W., Herjanic, B., Jung, K. G., & Amado, H. (1987). Reliability, validity, and parent-child agreement studies of the Diagnostic Interview for Children and Adolescents (DICA). *Journal of American Academy of Child Psychiatry*, 26, 649-653.
- Werry, J. S., & McCellan, J. M. (1992). Predicting outcome in child and adolescent (early onset) schizophrenia and bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 31, 147-150.
- Werry, J. S., McCellan, J. M., & Chard, L. (1991). Childhood and adolescent schizophrenic, bipolar, and schizoaffective disorders: A clinical and outcome study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 30, 457-465.
- Whitam, F. (1977). Childhood indicators of male homosexuality. *Archives of Sexual Behavior*, 6, 89-96.
- Whitam, F. L., Diamond, M., & Martin, J. (1993). Homosexual orientation in twins: a report on 61 pairs and three triplet sets. *Archives of Sexual Behavior*, 12, 207-226.
- Wilson, I., Griffin, C., & Wren, B. (2002). The validity of the diagnosis of gender identity disorder (child and adolescent criteria). *Clinical Child Psychology and Psychiatry*, 7, 335-351.
- World Health Organization. (1993). *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva: Author.
- Yunger, J. L., Carver, P. R., & Perry, D. G. (2004). Does gender identity influence children's psychological well-being? *Developmental Psychology*, 40, 572-582.

Zietsch, B. P., Verweij, K. J., Heath, A. C., Madden, P. A., Martin, N. G., Nelson, E. C., & Lynskey, M. T. (2012). Do shared etiological factors contribute to the relationship between sexual orientation and depression? *Psychological Medicine*, 42, 521-532.

Zimmerman, M., Rothschild, L., & Chelminski, L. (2005). The prevalence of DSM-IV personality disorders in psychiatric outpatients. *American Journal of Psychiatry*, 16, 1911-1918.

Zucker, K. J. (1985). Cross-gender identified children. In B. W. Steiner (Ed.), *Gender dysphoria: Development, research, and management* (pp. 75-174). New York: Plenum Press.

Zucker, K. J. (1992). Gender identity disorder. In S. R. Hooper, G. W. Hynd, & R. E. Mattison (Eds.), *Child psychopathology: Diagnostic criteria and clinical assessment* (pp. 305-342). Hillsdale, NJ: Erlbaum.

Zucker, K. J. (1994). Gender identity disorder in children. *MEDICINE North America*, 17, 373-375.

Zucker, K. J. (1999a). Commentary on Richardson's (1996) "Setting limits on gender health". *Harvard Review of Psychiatry*, 7, 37-42.

Zucker, K. J. (1999b). Gender identity disorder in the DSM-IV [Letter to the Editor]. *Journal of Sex and Marital Therapy*, 25, 5-9.

Zucker, K. J. (2000). Gender identity disorder. In A. J. Sameroff, M. Lewis, & S. M. Miller (Eds.), *Handbook of developmental psychopathology* (pp. 671-686). New York: Kluwer Academic/Plenum Publishers.

Zucker, K. J. (2001a). Gender identity disorder in children and adolescents. In G. O. Gabbard (Ed.), *Treatments of psychiatric disorders* (3rd ed., Vol. 2, pp. 2069-2094). Washington, DC: American Psychiatric Press.

Zucker, K. J. (2001b). Biological influences on psychosexual differentiation. In R. K. Unger (Ed.), *Handbook of the psychology of women and gender* (pp. 101-115). New York: John Wiley & Sons.

Zucker, K. J. (2002). Gender identity disorder. In M. Rutter & E. Taylor (Eds.), *Rutter's child and adolescent psychiatry* (pp. 737-753). Oxford: Blackwell Publishing.

Zucker, K. J. (2004a). Gender identity development and issues. *Child and Adolescent Psychiatric Clinics of North America*, 13, 551-568.

Zucker, K. J. (2004b). Gender identity disorder. In I. B. Weiner (Ed.), *Adult psychopathology case studies* (pp. 207-228). New York: Wiley.

Zucker, K. J. (2005a). Gender identity disorder in girls. In D. J. Bell, S. L. Foster, & E. J. Mash (Eds.), *Handbook of behavioral and emotional problems in girls* (pp. 285-319). New York: Kluwer Academic/Plenum Publishers.

Zucker, K. J. (2005b). Measurement of psychosexual differentiation. *Archives of Sexual Behavior*, 34, 375-388.

Zucker, K. J. (2005c). Gender identity disorder in children and adolescents. *Annual Review of Clinical Psychology*, 1, 467-492.

Zucker, K. J. (2006a). Gender identity disorder. In D. A. Wolfe & E. J. Mash (Eds.), *Behavioral and emotional disorders in adolescents: Nature, assessment, and treatment*. (pp. 535-562). New York: Guilford Press.

Zucker, K. J. (2006b). Commentary on Langer and Martin's (2004) "How dresses can make you mentally ill: Examining gender identity disorder in children." *Child and Adolescent Social Work Journal*, 23, 533-555.

Zucker, K. J. (2006c). "I'm a half-boy, half-girl": Play psychotherapy and parent counselling for gender identity disorder. In R. L. Spitzer, M. B. First, J. B. W. Williams, & M. Gibbons (Eds.), *DSM-IV-TR casebook, Vol. 2. Experts tell how they treated their own patients* (pp. 321-334). Washington, DC: American Psychiatric Publishing.

Zucker, K. J. (2007). Gender identity disorder in children, adolescents, and adults. In G. Gabbard (Ed.), *Gabbard's treatment of psychiatric disorders* (4th ed.) (pp. 683-701). Washington, DC: American Psychiatric Press.

Zucker, K. J. (2008a). Gender identity. In M. L. Wolraich, D. D. Drotar, P. H. Dworkin, & E. C. Perrin (Eds.), *Developmental-behavioral pediatrics: Evidence and practice* (pp. 825-839). Philadelphia: Mosby/Elsevier.

Zucker, K. J. (2008b). Children with gender identity disorder: Is there a best practice? [Enfants avec troubles de l'identité sexuée: y-a-t-il une pratique la meilleure?] *Neuropsychiatrie de l'Enfance et de l'Adolescence*, 56, 358-364.

Zucker, K. J., (2008c). Reflections on the relation between sex-typed behavior in childhood and sexual orientation in adulthood. *Journal of Gay & Lesbian Mental Health*, 12, 29-59.

Zucker, K. J. (2010a). The DSM diagnostic criteria for gender identity disorder in children. *Archives of Sexual Behavior*, 39, 477-498.

Zucker, K. J. (2010b). Gender identity and sexual orientation. In M. K. Dulcan (Ed.),

Dulcan's textbook of child and adolescent psychiatry (pp. 543-552). Washington, DC:

American Psychiatric Publishing.

Zucker, K. J., Allin, S., Babul-Hirji, R., Bradley, S. J., Chitayat, D., Khoury, A. E., et al.

(2003). Assessment of gender identity and gender role behaviour: A comparison of girls with gender identity disorder, girls exposed prenatally to gender-atypical levels of androgens, and control girls [Abstract]. *The Endocrinologist*, 13, 291.

Zucker, K. J., & Bradley, S. J. (1995). *Gender identity disorder and psychosexual problems in children and adolescents*. New York: Guilford Press.

Zucker, K. J., & Bradley, S. J. (2004). Gender identity and psychosexual disorders. In J. M.

Wiener & M. K. Dulcan (Eds.), *Textbook of child and adolescent psychiatry* (3rd ed.)

(pp. 813-835). Washington, DC: American Psychiatric Publishing.

Zucker, K. J., Bradley, S. J., Ben-Dat, D. N., Ho, C., Johnson, L., & Owen, A. (2003).

Psychopathology in the parents of boys with gender identity disorder [Letter to the Editor]. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42, 2-4.

Zucker, K. J., Bradley, S. J., Kuskis, M., Pecore, K., Birkenfeld-Adams, A., Doering,

...Wild, J. (1999). Gender constancy judgments in children with gender identity disorder: Evidence for a developmental lag. *Archives of Sexual Behavior*, 28, 475-502.

Zucker, K. J., Bradley, S. J., & Lowry Sullivan, C. B. (1996b). Traits of separation anxiety in

boys with gender identity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35, 791-798.

- Zucker, K. J., Bradley, S. J., Lowry Sullivan, C. B., Kuksis, M., Birkenfeld-Adams, A., & Mitchell, J. N. (1993). A gender identity interview for children. *Journal of Personality Assessment, 61*, 443-456.
- Zucker, K. J., Bradley, S. J., Oliver, G., Blake, J., Fleming, S., & Hood, J. (1996a). Psychosexual development of women with congenital adrenal hyperplasia. *Hormones and behavior, 30*, 300-318.
- Zucker, K. J., Bradley, S. J., Owen-Anderson, A., Kibblewhite, S. J., & Cantor, J. M. (2008). Is gender identity disorder in adolescents coming out of the closet? [Letter to the Editor]. *Journal of Sex and Marital Therapy, 34*, 287-290.
- Zucker, K. J., Bradley, S. J., Owen-Anderson, A., Kibblewhite, S. J., Wood, H., Singh, D., & Choi, K. (2012a). Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. *Journal of Sex and Marital Therapy, 38*, 151-189.
- Zucker, K. J., Bradley, S. J., Owen-Anderson, A., Singh, D., Blanchard, R., & Bain, J. (2011). Puberty-blocking hormonal therapy for adolescents with gender identity disorder: A descriptive clinical study. *Journal of Gay & Lesbian Mental Health, 15*, 58-82.
- Zucker, K. J., Bradley, S. J., Owen-Anderson, A., & Singh, D. (2010b, April). *A parent-report Gender Identity/Gender Role Questionnaire for Adolescents*. Poster presented at the Fourth Gender Development Research Conference, San Francisco, CA.
- Zucker, K. J., Bradley, S. J., & Sanikhani, M. (1997). Sex differences in referral rates of children with gender identity disorder: Some hypotheses. *Journal of Abnormal Child Psychology, 25*, 21

Zucker, K. J., Bradley, S. J., Sullivan, C. B., Kuskis, M., Birkenfeld-Adams, & Mitchell, J.

N. (1993). A gender identity interview for children. *Journal of Personality Assessment*, 61, 443-456.

Zucker, K. J., & Cohen-Kettenis, P. T. (2008). Gender identity disorder in children and adolescents. In D. L. Rowland & L. Incrocci (Eds.), *Handbook of sexual and gender identity disorders* (pp. 376-422). New York: Wiley.

Zucker, K. J., Doering, R. W., Bradley, S. J., & Finegan, J. K. (1982). Sex-typed play in gender-disturbed children: A comparison to sibling and psychiatric controls. *Archives of Sexual Behavior*, 11, 309-321.

Zucker, K. J., Drummond, K. D., Bradley, S. J., & Peterson-Badali, M. (2009). Troubled mediations on psychosexual differentiations: Reply to Hegarty (2009). *Developmental Psychology*, 45, 904-908.

Zucker, K. J., Finegan, J. K., Doering, R. W., & Bradley, S. J. (1983). Human figure drawings of gender-problem children: A comparison to siblings, psychiatric, and normal controls. *Journal of Abnormal Child Psychology*, 11, 287-298.

Zucker, K. J., & Green, R. (1992). Psychosexual disorders in children and adolescents. *Journal of Child Psychology and Psychiatry*, 33, 107-151.

Zucker, K. J., & Lawrence, A. A. (2009). Epidemiology of gender identity disorder: Recommendations for the *Standards of Care* of the World Professional Association for Transgender Health. *International Journal of Transgenderism*, 11, 8-18.

Zucker, K. J., Lozinski, J. A., Bradley, S. J., & Doering, R. W. (1992). Sex-typed responses in the Rorschach protocols of children with gender identity disorder. *Journal of Personality Assessment*, 58, 295-310.

Zucker, K. J., Mitchell, J. N., Bradley, S. J., Tkachuk, J., Cantor, J. M., & Allin, S. M.

(2006). The Recalled Childhood Gender Identity/Gender Role Questionnaire:

Psychometric properties. *Sex Roles*, 54, 469-483.

Zucker, K. J., Owen, A., Bradley, S. J., & Ameeriar, L. (2002). Gender-dysphoric children and adolescents: A comparative analysis of demographic characteristics and behavior problems. *Clinical Child Psychology and Psychiatry*, 7, 398-411.

Zucker, K. J., & Seto, M. C. (2008). Gender identity and sexual disorders. In M. Rutter, D. V. M. Bishop, D. S. Pine, S. Scott, J. Stenvenson, E. Taylor, & A. Thapar (Eds.), *Rutter's child and adolescent psychiatry* (pp. 864-881). Oxford: Blackwell Publishing.

Zucker, K. J., & Spitzer, R. L. (2005). Was the gender identity disorder of childhood diagnosis introduced into DSM-III as a backdoor maneuver to replace homosexuality? A historical note. *Journal of Sex & Marital Therapy*, 31, 31-42.

Zucker, K. J., Wilson-Smith, D. N., Kurita, J. A., & Stern, A. (1995). Children's appraisals of sex-typed behavior in their peers. *Sex Roles*, 33, 703-725.

Zucker, K. J., Wood, H., Singh, D., & Bradley, S. J. (2012b). A developmental biopsychosocial model for the treatment of children with gender identity disorder. *Journal of Homosexuality*, 59, 369-397.

Zuger, B. (1978). Effeminate behavior present in boys from childhood: Ten additional years of follow-up. *Comprehensive Psychiatry*, 19, 363-369.

Appendix A

DSM-IV-TR Diagnostic Criteria for Gender Identity Disorder

DSM-IV-TR Diagnostic Criteria for Gender Identity Disorder

-
- A. A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex.

In children, the disturbance is manifested by four (or more) of the following:

1. Repeatedly stated desire to be, or insistence that he or she is, the other sex.
2. In boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing.
3. Strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex.
4. Intense desire to participate in the stereotypical games and pastimes of the other sex.
5. Strong preference for playmates of the other sex.

In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex.

- B. Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex.

In children, the disturbance is manifested by any of the following:

In boys: assertion that his penis or testes are disgusting or will disappear or assertion that it would be better not to have a penis, or aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities.

In girls: rejection of urinating in a sitting position, assertion that she has or will grow a penis, or assertion that she does not want to grow breasts or menstruate or marked aversion toward normative female clothing.

In adolescents and adults, the disturbance is manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex.

- C. The disturbance is not concurrent with a physical intersex condition.

- D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note. From the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition-Text Revision (p. 581). Copyright 2000 by the American Psychiatric Association.

Appendix B

Proposed DSM-5 Diagnostic Criteria for Gender Dysphoria in Children

Proposed DSM-5 Diagnostic Criteria for Gender Dysphoria (in Children)⁶⁵

-
- A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by at least 6 of the following indicators (including A1):
1. A strong desire to be of the other gender or an insistence that he or she is the other gender (or some alternative gender different from one's assigned gender)
 2. In boys, a strong preference for cross-dressing or simulating female attire; in girls, a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing
 3. A strong preference for cross-gender roles in make-believe or fantasy play
 4. A strong preference for the toys, games, or activities typical of the other gender
 5. A strong preference for playmates of the other gender
 6. In boys, a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; in girls, a strong rejection of typically feminine toys, games, and activities
 7. A strong dislike of one's sexual anatomy
 8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender
- B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning, or with a significantly increased risk of suffering, such as distress or disability.

Subtypes

With a disorder of sex development

Without a disorder of sex development

⁶⁵ *Note.* American Psychiatric Association. (2011). DSM-5 development. Retrieved from www.dsm5.org/ProposedRevision/Pages/proposedrevision.aspx?rid=192. Proposed criteria as of May 4, 2011.

Appendix C

Phone Script

I: Interviewer (Devita Singh)

P: Parent of Potential Participant

I: Hello, may I speak to (name of parent). My name is Devita Singh. I work with Dr. Ken Zucker from the Centre for Addiction and Mental Health. Dr. Zucker last saw you and (name of participant) in (give year). [For those participants last seen before 1997, I will indicate that we used to be called the Clarke Institute of Psychiatry].

P: Hi. How are you?

I: I am fine, thank you. Let me explain why I am calling you. Right now, Dr. Zucker and I are doing a follow-up project on all the boys that have been seen in our clinic over the years and who are now at least 17 years old⁶⁶. We are interested in finding out how children who were seen in the clinic are doing now. Because (name of participant) was a minor when he was first assessed by Dr. Zucker, I wanted to speak with you first about asking (name of participant) if he would be willing to speak with me over the telephone to hear about our project and then deciding if he would like to be a part of it.

P: Can you tell me more about what the study is about?

I: Of course. The purpose of the project is for us to find out how the youngsters we have seen over the years are doing with regard to their gender, sexuality, and overall emotional well-being. We would ask (name of participant) to come to the Centre for about 5 hours, including breaks. During this time, (name of participant) will meet with me. I am a student at the University of Toronto who is working with Dr. Zucker. During our meeting, (name of participant) will be interviewed about his gender identity and sexual development asked to complete some psychological tests and questionnaires. If it is ok with (name of participant), we would also ask you to complete two questionnaires about (name of participant) behavior, which we would mail to you. We will be able to provide some financial compensation for (name of participant's) participation, including covering costs of transportation.

P: Yes, that is fine with me.

I: Ok. Should I speak with (name of participant) now or would you like to talk with him first and I can call back tomorrow?

⁶⁶ For potential participants who were last seen when they were over the age of 16, they will be contacted directly and the script modified accordingly.

Appendix D

Vignette: Parent Report on Gender Identity and Sexual Orientation

Damon was initially assessed in the Gender Identity Service when he was 5 years old.

Damon's mother, Ms. Salvator, was contacted for follow-up when Damon was 22-years-old. Ms. Salvator indicated that Damon no longer lived with her and agreed to inform Damon that we were interested in conducting a follow-up assessment with him. It was very difficult for Ms. Salvator to contact Damon as he did not have a permanent address or telephone and was living temporarily with various friends. Her only means of contacting was through email. After several months of attempted contact, Damon indicated to his mother that he was not interested in participating in the follow-up study but was comfortable with his mother providing us with information.

Ms. Salvator explained that her and Damon's life had been chaotic. Damon dropped out of high school when he was 16 years old and moved out of his mother's home four years thereafter. Ms. Salvator had not seen Damon since he left her home. To the best of Ms. Salvator's knowledge, Damon never had paid employment. Regarding gender identity and sexual orientation, Ms. Salvator stated that Damon was living as a gay male and was very involved with the gay community. She added that Damon had been open about his sexuality for several years and appeared to be happy with his biological status as male. Ms. Salvator reported that Damon's twin sibling died of a possible drug-overdose about two years after Damon left high school. Ms. Salvator reported that Damon "never recovered" from his sibling's death.

Based on the information obtained from Damon's mother, Damon was classified as a desister with regard to gender identity and as homosexual in sexual orientation.

Appendix E

Participant-Initiated Research Contact

Reasons for Clinical Contact

Participant-Initiated Clinical Contact

Participant ID	Year of Follow-up	Age at Follow-up	Reason for Clinical Contact
1	1995	18.82	Gender dysphoria
2	1997	15.50	Other clinical reasons: depression, school phobia
3	1998	18.10	Other clinical reasons: depression, conflicted about sexual attraction to old men, curiosity about the purpose of the childhood assessment
4	2000	16.01	Sexual orientation
5	2000	16.63	Other clinical reasons: parent-child conflict
6	2002	20.09	Sexual orientation
7	2002	15.46	Other clinical reasons: social problems
8	2002	13.62	Gender dysphoria
9	2002	16.90	Gender dysphoria and sexual orientation
10	2003	22.53	Sexual orientation
11	2003	23.55	Gender dysphoria
12	2003	16.26	Other clinical reasons: alcohol abuse, poor academic performance
13	2003	17.11	Other clinical reasons: depression
14	2004	27.13	Other clinical reasons: substance dependence
15	2004	18.70	Other clinical reasons: depression
16	2004	20.35	Other clinical reasons: depression
17	2005	17.06	Other clinical reasons: behavior problems
18	2005	18.47	Other clinical reasons: behavior problems
19	2005	16.20	Sexual orientation and other clinical reasons: ADHD, learning difficulties
20	2006	16.97	Other clinical reasons: learning disability
21	2007	13.07	Gender dysphoria
22	2007	15.97	Gender dysphoria

Participant-Initiated Clinical Contact

Participant ID	Year of Follow-up	Age at Follow-up	Reason for Clinical Contact
23	2008	16.84	Other clinical reasons: substance abuse, poor academic performance, anxiety
24	2008	16.61	Gender dysphoria
25	2009	15.53	Other clinical reasons: learning disability, anxiety
26	2009	17.68	Gender dysphoria
27	2009	16.01	Other clinical reasons: substance abuse, conduct disorder
28	2009	17.18	Other clinical reasons: medication reassessment
29	2010	15.41	Other clinical reasons: social withdrawal, poor academic performance
30	2010	14.51	Other clinical reasons: alcohol use
31	2011	15.09	Sexual orientation
32	2011	16.23	Sexual orientation

Appendix F

Research Consent Form

RESEARCH CONSENT FORM

Title of Research Project: Gender Identity and Psychosocial Development

Investigators: Kenneth J. Zucker, Ph.D., Primary Investigator (416-535-8501 x 4040)
Devita Singh, M.A., Co-Investigator (416-535-8501 x 4175)

Devita Singh or Dr. Zucker has explained that the purpose of this study is to gain a better understanding of gender identity development into late adolescence or young adulthood. You will be asked questions about you in an interview and will also complete questionnaires and take some tests. Part of the interview will be about your sexual development and experiences. The interview will be recorded with a tape recorder. Your participation will take place in a quiet room at the Centre for Addiction and Mental Health. The following points have been explained:

1. Your participation will include the following: during a single session, you will complete a total of 8 paper-and-pencil questionnaires, 1 interview, and 2 tests. The session will last for approximately 5 hours, including breaks.
2. You have the right to refuse to answer any questions.
3. Participation in this research is voluntary. You can withdraw your participation at any time, even after beginning an interview or task.
4. All of the information collected will remain strictly confidential. Only people associated with the study will see your responses. This consent form will be stored separately from all other information that you have provided. Your responses will not be associated with your name; instead, your name will be converted to a code number on all questionnaires and forms.
5. Your privacy will be protected in any scientific presentation or publication resulting from this study. The audio recording of your interview will only be used to record your responses. The tapes will then be destroyed.
6. You will receive \$___ for compensation of your time.
7. With your consent, we will also contact your parent or guardian to complete a questionnaire about your development.
8. Information that you provide about yourself will be kept confidential and stored using a code number that does not include your name. The audiotape of your interview will be stored in a locked filing cabinet. The audiotapes will be retained for 5 years after the completion of any scientific publications that result from this study, and at that time, they will be destroyed.

9. The investigator will answer any questions about the research now or during the course of the study. If you have any other questions or concerns, you can address them to the primary investigator, Dr. Kenneth Zucker (416-535-8501, extension 4040) or the co-investigator, Devita Singh (416-535-8501 x 4175). You will be given a copy of this consent form for your records.
10. Dr. Padraig Darby, Chair, Research Ethics Board, Centre for Addiction and Mental Health, may be contacted by research subjects to discuss their rights. Dr. Darby may be reached by telephone at 416-535-8501, extension 6876.
11. As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board and, if applicable, by the Health Canada Therapeutic Products Programme. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you must maintain your confidentiality to the extent permitted by law.

I consent to participate in this study and I consent to allow my parents or guardian to complete a questionnaire about me.

Name of Participant (Please Print)

Signature of Participant

Date

Name of Person Obtaining Consent (Please Print)

Signature of Person Obtaining Consent

Date

Appendix G

Semi-Structured Interview to Assess Gender Identity Disorder in Biological Males

Semi-Structured Interview for Gender Identity Disorder

Timeframe: Past 12 months

Point A Criteria

1. In the past 12 months, have you felt like you wanted to be a woman?

____ YES ____SOMETIMES ____NO

If YES or SOMETIMES, Ask:

- a. How often do you have these feelings of wanting to be a woman?
- b. Describe what it is that makes you feel this way.
- c. Are there situations where you find these feelings stronger or more intense?
If YES, ask to elaborate.
- d. Are there times in the past 12 months when you have felt confused as to whether you wanted to be a man or a woman?
If YES, ask to elaborate.

2. Have you ever told anyone that you wanted to be a woman?

____ YES ____SOMETIMES ____NO

3. Do you frequently pass as the other sex?

____ YES ____SOMETIMES ____NO

If YES or SOMETIMES, ASK:

- a. In what type of situations do you present yourself as a woman? (social situations, internet, etc)
 - b. How? (e.g., clothing)
 - c. How often do you present yourself as a woman?
4. Do you have the desire to live and/or be treated as the opposite sex?

____ YES ____SOMETIMES ____NO

5. Do you believe that you have the typical feelings and reactions of the opposite sex?

___ YES ___SOMETIMES ___NO

Point B Criteria

1. Would you like to receive sex hormones to feminize your physical appearance (e.g., to grow breasts; to not have body hair)?

___ YES ___SOMETIMES ___NO

2. Would you like to have surgery to create a vagina?

___ YES ___SOMETIMES ___NO

3. Would you like to get rid of male sex characteristics, such as your penis or testes?

___ YES ___SOMETIMES ___NO

IF YES or SOMETIMES to 1, 2, or 3 above, Ask:

Have you seen a doctor to request hormones or surgery?

If YES, ask to elaborate.

4. Do you believe that you should have been born a female?

___ YES ___SOMETIMES ___NO

Distress Criteria

1. Do these feelings about your gender cause you significant stress in social life? If YES, how?

2. Do these feelings about your gender identity cause you significant stress in your occupational life (e.g., job, school, etc.)? If YES, how?

Appendix H

Inter-rater Reliability for Kinsey Ratings of Sexual Fantasy and Sexual Behavior

Kappa Statistics For Kinsey Sexual Fantasy Ratings

Variable	Kappa
Crush	1.00
Visual	0.94
Dreams	1.00
Masturbation	0.81
Global Fantasy Rating	0.95

Kappa Statistics For Kinsey Sexual Behavior Ratings

Variable	Kappa
Dating	1.00
Holding hands	0.91
Kissing	1.00
Genital/breast contact	1.00
Intercourse	1.00
Global Behavior Rating	1.00

Appendix I

Suicidality Questionnaire

Suicidality Questionnaire

These questions ask about feelings or behaviors about hurting yourself.

The next six questions will be about any feelings or thoughts you have had since the age of 13.

1. Since the age of 13, have you *ever seriously* considered attempting suicide?
 - a. Never
 - b. Rarely
 - c. Sometimes
 - d. Often

2. Did you make a plan about how you would attempt suicide?
 - a. Yes
 - b. No

3. Since the age of 13, how many times did you actually attempt suicide?
 - a. 0 times
 - b. 1 time
 - c. 2 or 3 times
 - d. 4 or 5 times
 - e. 6 or more times

4. If you have attempted suicide in the past, did your attempt result in an injury, poisoning, or overdose that had to be treated by a doctor or nurse?
 - a. I did not attempt suicide in the past
 - b. Yes
 - c. No

5. If you attempted suicide since you were 13, how did you feel at the time you tried to attempt suicide?
 - a. I knew I was not going to die.
 - b. I really wanted to die.

6. Have your feelings about suicide been related to your unhappiness about being a male.
 - a. Very much related
 - b. Somewhat related
 - c. A little related
 - d. Not at all related

The next questions are similar but will be about your feelings and thoughts within the *past 12 months*.

1. During the past 12 months, did you *ever seriously* consider attempting suicide?
 - a. Never
 - b. Rarely
 - c. Sometimes
 - d. Often
2. During the past 12 months, did you make a plan about how you would attempt suicide?
 - a. Yes
 - b. No
3. During the past 12 months, how many times did you actually attempt suicide?
 - a. 0 times
 - b. 1 time
 - c. 2 or 3 times
 - d. 4 or 5 times
 - e. 6 or more times
4. If you attempted suicide during the past 12 months, did your attempt result in an injury, poisoning, or overdose that had to be treated by a doctor or nurse?
 - a. I did not attempt suicide in the past 12 months
 - b. Yes
 - c. No
5. If you attempted suicide in the past 12 months, how did you feel at the time you tried to attempt suicide.
 - a. I knew I was not going to die.
 - b. I really wanted to die.
6. How do you feel now?
 - a. I am glad to be alive.
 - b. I wish I had been successful.
7. Have your feelings about suicide been related to your unhappiness about being a male?
 - a. Very much related
 - b. Somewhat related
 - c. A little related
 - d. Not at all related

Appendix J

Victimization Survey

Victimization Survey

Since the age of 13, how often have these things happened to you because of your gender identity?

	Never	Once	Twice	3 or more	If more than 3, how many?
a. Verbal insults	0	1	2	3	_____
b. Someone threatened to tell others about your gender identity	0	1	2	3	_____
c. Threats of physical violence	0	1	2	3	_____
d. Objects thrown at you	0	1	2	3	_____
e. Punched, kicked or beaten	0	1	2	3	_____
f. Threatened with a knife, gun, or another weapon	0	1	2	3	_____
g. Sexually attacked	0	1	2	3	_____

In the **past 12 months**, how often have these things happened to you because of your gender identity?

	Never	Once	Twice	3 or more	If more than 3, how many?
a. Verbal insults	0	1	2	3	_____
b. Someone threatened to tell others about your gender identity	0	1	2	3	_____
c. Threats of physical violence	0	1	2	3	_____
d. Objects thrown at you	0	1	2	3	_____
e. Punched, kicked or beaten	0	1	2	3	_____
f. Threatened with a knife, gun, or another weapon	0	1	2	3	_____
g. Sexually attacked	0	1	2	3	_____

If you scored Never for verbal insults OR threats to tell others about your gender identity on the first page, skip this page and continue on page 3 (the next page).

Of all the times you were verbally insulted, where did these incidents occur (check off the applicable locations)?

- | | |
|--|--|
| <input type="checkbox"/> Home | <input type="checkbox"/> Social settings (e.g., bars, parks, etc.) |
| <input type="checkbox"/> High school | <input type="checkbox"/> College Campus |
| <input type="checkbox"/> Neighbourhood | <input type="checkbox"/> Work place |
| <input type="checkbox"/> Other: _____ | |

Of all the times you were ever verbally insulted, how many incidents were done by:

Relationship (Check if YES, did it)	How many times?	Relationship (Check if YES, did it)	How many times?
<input type="checkbox"/> Mother	_____	<input type="checkbox"/> Male strangers	_____
<input type="checkbox"/> Father	_____	<input type="checkbox"/> Female strangers	_____
<input type="checkbox"/> Stepmother	_____	<input type="checkbox"/> Teachers	_____
<input type="checkbox"/> Stepfather	_____	<input type="checkbox"/> Physical education teachers	_____
<input type="checkbox"/> Your mother's girlfriend or boyfriend	_____	<input type="checkbox"/> Boyfriends	_____
<input type="checkbox"/> Your father's girlfriend or boyfriend	_____	<input type="checkbox"/> Girlfriends	_____
<input type="checkbox"/> Your brother(s)	_____	<input type="checkbox"/> Houseparents (in group home)	_____
<input type="checkbox"/> Your sister(s)	_____	<input type="checkbox"/> Fosterparents	_____
<input type="checkbox"/> Other members of the family	_____	<input type="checkbox"/> Counselors	_____
<input type="checkbox"/> Male peer who was neither a friend nor a stranger	_____	<input type="checkbox"/> Other people: _____	_____
<input type="checkbox"/> Female peer who neither a friend nor a stranger	_____	<input type="checkbox"/> Other people: _____	_____
<input type="checkbox"/> Male friends	_____	<input type="checkbox"/> Female friends	_____

If you scored *Never* for any physical violence (e.g., physical threats, objects thrown, punched, kicked, or beaten, and threats with weapons) on the first page, skip this page and continue on page 4 (the next page).

Of all the times you were threatened with physical violence, where did these incidents occur (check off the applicable locations)?

- | | |
|--|--|
| <input type="checkbox"/> Home | <input type="checkbox"/> Social settings (e.g., bars, parks, etc.) |
| <input type="checkbox"/> High school | <input type="checkbox"/> College Campus |
| <input type="checkbox"/> Neighbourhood | <input type="checkbox"/> Work place |
| <input type="checkbox"/> Other: _____ | |

Of all the times you were every threatened with physical violence, how many incidents were done by:

Relationship (Check if YES, did it)	How many times?	Relationship (Check if YES, did it)	How many times?
<input type="checkbox"/> Mother	_____	<input type="checkbox"/> Male strangers	_____
<input type="checkbox"/> Father	_____	<input type="checkbox"/> Female strangers	_____
<input type="checkbox"/> Stepmother	_____	<input type="checkbox"/> Teachers	_____
<input type="checkbox"/> Stepfather	_____	<input type="checkbox"/> Physical education teachers	_____
<input type="checkbox"/> Your mother's girlfriend or boyfriend	_____	<input type="checkbox"/> Boyfriends	_____
<input type="checkbox"/> Your father's girlfriend or boyfriend	_____	<input type="checkbox"/> Girlfriends	_____
<input type="checkbox"/> Your brother(s)	_____	<input type="checkbox"/> Houseparents (in group home)	_____
<input type="checkbox"/> Your sister(s)	_____	<input type="checkbox"/> Fosterparents	_____
<input type="checkbox"/> Other members of the family	_____	<input type="checkbox"/> Counselors	_____
<input type="checkbox"/> Male peer who was neither a friend nor a stranger	_____	<input type="checkbox"/> Other people:	_____
<input type="checkbox"/> Female peer who neither a friend nor a stranger	_____	<input type="checkbox"/> Other people:	_____
<input type="checkbox"/> Male friends	_____	<input type="checkbox"/> Female friends	_____

If you scored *Never* for sexual attacks on the first page, skip this page and continue on page 5 (the next page).

Of all the times you were attacked sexually, where did these incidents occur (check off the applicable locations)?

- | | |
|--|--|
| <input type="checkbox"/> Home | <input type="checkbox"/> Social settings (e.g., bars, parks, etc.) |
| <input type="checkbox"/> High school | <input type="checkbox"/> College Campus |
| <input type="checkbox"/> Neighbourhood | <input type="checkbox"/> Work place |
| <input type="checkbox"/> Other: _____ | |

Of all the times you were ever attacked sexually, how many incidents were done by?

Relationship (Check if YES, did it)	How many times?	Relationship (Check if YES, did it)	How many times?
<input type="checkbox"/> Mother	_____	<input type="checkbox"/> Male strangers	_____
<input type="checkbox"/> Father	_____	<input type="checkbox"/> Female strangers	_____
<input type="checkbox"/> Stepmother	_____	<input type="checkbox"/> Teachers	_____
<input type="checkbox"/> Stepfather	_____	<input type="checkbox"/> Physical education teachers	_____
<input type="checkbox"/> Your mother's girlfriend or boyfriend	_____	<input type="checkbox"/> Boyfriends	_____
<input type="checkbox"/> Your father's girlfriend or boyfriend	_____	<input type="checkbox"/> Girlfriends	_____
<input type="checkbox"/> Your brother(s)	_____	<input type="checkbox"/> Houseparents (in group home)	_____
<input type="checkbox"/> Your sister(s)	_____	<input type="checkbox"/> Fosterparents	_____
<input type="checkbox"/> Other members of the family	_____	<input type="checkbox"/> Counselors	_____
<input type="checkbox"/> Male peer who was neither a friend nor a stranger	_____	<input type="checkbox"/> Other people:	_____
<input type="checkbox"/> Female peer who neither a friend nor a stranger	_____	<input type="checkbox"/> Other people:	_____
<input type="checkbox"/> Male friends	_____	<input type="checkbox"/> Female friends	_____

If you have been the target of harassment, threats, or violence because of your gender identity have you always reported it to an appropriate official (e.g., teacher, police, job supervisor)?

- a. Not applicable
- b. No, I never reported any incidents.
- c. No, but I have reported some. How many? _____
- d. Yes, I reported all incidents. How many? _____

Have you changed the way you act in any way because of fears of being harassed or attacked because of your gender identity (e.g., avoid certain locations or social groups)?

- a. No
- b. Yes
How have you changed your behavior? Please write below.

Thinking back on any of these incidents, how upset do you get when you think about it now?

- a. Not at all
- b. Some
- c. A lot

How have the incidents affected the way you saw your future?

- a. Made no difference
- b. Made me worry about the future
- c. Made me wonder if life was worth living

Appendix K

Gender Identity and Sexual Orientation at Follow-up

Gender Identity and Sexual Orientation at Follow-up

No.	FU Date(s) ^a	Age at Assessment (in years)	Age at follow-up (in years)	Kinsey Ratings		DSM
				Fantasy	Behavior	
1	1987-11-16	6.42	18.24	6	6	+
2	1986-01-03	5.69	15.05	0	0	+
3	1987-10-23	8.23	17.73	0	0	-
4	1986-01-28 ^a	6.39	15.15	6	6	+
	1990-03-14		18.27			
	2011-01-28		39.15			
5	1986-07-08 ^a	5.87	14.06	0	7	+
	1987-07-27		15.11			
6	1987-02-04 ^a	5.42	14.15	7	7	+
	1989-03-13		16.26			
7	1986-08-05	9.53	17.65	0	7	-
8	1987-07-03 ^a	5.07	13.96	0	7	+
	1988-12-03		15.39			
9	1986-12-19	7.95	16.10	0	0	-
10	1986-03-25	12.85	20.14	5	6	-
11	1987-11-16 ^a	5.33	14.15	5	7	+
	1990-07-15		16.80			
	1993-12-15		20.23			
12	1986-02-11 ^a	8.79	15.82	3	7	+
	1987-02-11		16.82			
	1989-04-27		19.04			
13	1987-04-22	6.19	14.22	7	7	+
14	1989-03-16 ^a	4.69	14.46	0	7	-
	1988-12-29		14.25			

No.	FU Date(s) ^a	Age at Assessment (in years)	Age at follow-up (in years)	Kinsey Ratings		DSM
				Fantasy	Behavior	
15	1986-06-24	10.38	17.32	0	0	-
16	1983-11-02 ^a	7.00	11.14	0	0	+
	1986-11-30		14.21			
17	1987-03-19	7.19	14.68	0	0	+
18	1986-07-21	12.37	18.84	1	0	-
19	1986-04-15 ^a	10.70	17.09	6	6	-
	1988-11-07		19.38			
20	1988-02-02	6.46	14.34	0	0	+
21	1988-10-12 ^a	5.85	13.31	6	6	+
	1992-02-15		17.65			
	2010-08-09		35.14			
22	1991-12-19	5.14	15.83	0	7	+
23	1986-12-23 ^a	11.13	16.88	6	6	-
	1988-07-27		18.28			
	1993-11-16		23.59			
24	1986-12-22 ^a	10.49	16.03	6	6	-
	1990-01-11		19.08			
25	1993-04-01	5.34	20.00	6	6	+
26	1988-08-04	8.58	15.32	0	7	+
27	1987-08-06	11.07	16.74	3	4	+
28	1988-11-24	8.46	14.76	0	7	+
29	1991-12-02	5.61	14.96	0	7	-
30	1990-01-21	9.14	16.53	0	7	-
31	1992-03-23 ^a	3.75	13.09	5	3	+
	1998-10-15		19.65			

No.	FU Date(s) ^a	Age at Assessment (in years)	Age at follow-up (in years)	Kinsey Ratings		DSM
				Fantasy	Behavior	
32	1987-11-09	9.31	14.06	2	7	+
33	1986-02-04	12.29	15.06	3	7	-
34	2002-06-07	7.18	26.04	6	6	-
35	1990-10-15	11.01	17.95	0	7	-
36	1988-03-11	10.23	14.53	0	7	-
37	1990-07-26	8.58	15.01	0	0	+
38	2004-06-06	6.90	27.13	6	6	+
39	1988-03-07	10.71	14.63	5	7	-
40	1991-11-16	8.99	15.47	5	6	+
41	2009-02-23	3.77	27.51	5	5	+
42	1988-06-12	11.99	14.82	7	7	-
43	1991-12-20	9.68	16.03	0	0	-
44	2009-09-11	6.35	29.60	6	7	+
45	2003-08-20	5.59	22.53	6	6	+
46	2009-10-24	7.29	30.31	6	6	+
47	2009-07-29	4.72	27.29	6	6	+
48	1998-06-22	6.75	18.10	6	6	+
49	2003-06-04	8.22	23.55	6	6	+
50	2000-05-11	3.52	16.01	6	6	+
51	2002-07-03	5.91	20.09	4	6	+
52	2010-03-31	4.04	26.03	6	7	+
53	2010-01-22	6.94	28.70	5	6	+

No.	FU Date(s) ^a	Age at Assessment (in years)	Age at follow-up (in years)	Kinsey Ratings		DSM
				Fantasy	Behavior	
54	2010-01-25	4.96	26.67	6	6	-
55	2010-01-23	5.09	26.59	6	6	+
56	2010-09-20	4.15	26.08	1	0	+
57	2009-12-15	5.22	26.12	5	6	+
58	2010-04-28	6.33	26.26	6	6	+
59	2010-01-30	3.95	23.60	5	6	+
60	2010-02-08	6.73	26.08	6	6	+
61	2003-04-17	3.85	16.26	0	—	+
62	2004-08-26	5.13	18.70	6	6	+
63	2010-05-26	5.25	24.24	6	6	+
64	2010-05-19	4.67	23.50	3	4	-
65	1999-03-25 ^a	7.13	14.58	6	6	+
	2004-12-30		20.35			
66	2010-03-01	9.03	27.35	6	6	-
67	2002-08-29	5.19	16.29	6	1	+
68	2010-11-19	4.16	22.93	5	4	+
69	2000-08-31	8.11	16.63	2	7	-
70	2011-03-06	4.41	23.38	0	0	+
71	2009-08-18	4.32	21.65	6	6	+
72	2010-12-20	3.57	22.16	0	0	-
73	2003-10-08	6.58	17.11	6	6	-

No.	FU Date(s) ^a	Age at Assessment (in years)	Age at follow-up (in years)	Kinsey Ratings		DSM
				Fantasy	Behavior	
74	2009-03-23	6.95	22.87	6	6	+
75	2006-06-02	3.98	16.97	0	0	+
76	2009-01-31	6.82	21.98	5	6	+
77	2005-05-12	6.02	17.06	0	0	+
78	1997-04-10	12.67	15.50	7	7	-
79	2008-03-19	4.06	16.84	6	6	+
80	2009-11-23	7.45	22.32	2	0	+
81	2005-07-18 ^a	9.46	18.47	0	0	-
	2002-01-08		14.94			
	2001-05-30		14.35			
82	2002-08-30	9.47	15.46	0	0	-
83	2009-07-04	10.30	20.27	6	6	+
84	2002-08-28	8.87	13.62	6	6	+
85	2009-03-21	5.83	17.14	3	3	+
86	2009-02-08	4.31	15.53	5	7	+
87	2009-08-27	9.27	20.75	0	0	-
88	2009-06-13	7.62	19.77	6	6	+
89	2009-03-08	8.19	19.05	5	0	-
90	2009-11-22	8.66	20.05	3	0	+
91	2002-07-29	12.82	16.90	0	7	-
92	2009-10-02	9.07	20.25	0	0	-
93	2011-02-06	5.35	17.43	6	6	+

No.	FU Date(s) ^a	Age at Assessment (in years)	Age at follow-up (in years)	Kinsey Ratings		DSM
				Fantasy	Behavior	
94	2005-09-01	9.46	16.20	—	—	+
95	2010-12-15	10.35	22.18	6	6	+
96	2010-08-16	4.39	15.41	0	0	+
97	2011-02-09	3.69	15.09	4	0	+
98	2009-02-25	10.0	19.19	0	0	+
99	2010-07-19	4.53	14.51	0	7	+
100	2009-04-08	9.13	17.68	6	6	+
101	2011-03-02	6.39	16.23	1	0	+
102	2009-09-25	12.48	20.42	3	3	-
103	2009-09-12	8.84	16.01	3	3	+
104	2008-04-16	10.76	16.61	6	6	+
105	2009-12-18	12.99	20.22	0	7	-
106	2007-04-26	8.51	13.07	0	0	+
107	2010-07-10	11.53	18.96	5	6	+
108	2007-04-27 ^a	11.60	15.55	6	7	-
	2007-09-26		15.97			
109	2009-10-30	9.68	15.69	6	6	+
110	2009-11-21	12.84	17.18	0	0	-

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111	2010-11-09	3.75	31.28	—	—	+
112	1995-05-08	8.36	18.82	(6)	—	+

No.	FU Date(s) ^a	Age at Assessment (in years)	Age at follow-up (in years)	Kinsey Ratings		DSM
				Fantasy	Behavior	
113	2009-09-09	8.69	33.34	(6)	—	-
114	2009-06-29	5.48	28.73	(6)	—	-
115	2009-08-10	4.63	27.73	—	—	+
116	1995-12-15	7.30	16.67	(6)	—	-
117	2009-10-09	5.39	27.75	(6)	—	-
118	2010-08-19	5.88	28.11	(6)	—	-
119	2009-11-20	9.27	31.40	(6)	—	-
120	2009-08-10	7.82	29.57	(0)	—	-
121	2009-09-20	6.93	28.69	—	—	-
122	2009-11-17	3.33	24.77	(6)	—	+
123	2009-11-19	4.65	24.77	(0)	—	+
124	2010-01-11	6.16	25.60	(0)	—	+
125	2009-12-14	6.35	25.23	—	—	-
126	2009-09-21	5.28	23.65	(6)	—	+
127	2010-01-31	4.73	23.50	(0)	—	+
128	2001-11-15	11.14	21.58	(6)	—	-
129	2010-02-11	3.84	22.47	(6)	—	+
130	2003-06-15	11.24	23.16	(6)	—	-
131	2011-04-07	4.60	24.18	(6)	—	+
132	2010-03-10	10.21	28.15	—	—	-
133	2002-12-19	5.55	18.10	(6)	—	+
134	2009-02-04	10.18	21.55	(6)	—	+

No.	FU Date(s) ^a	Age at Assessment (in years)	Age at follow-up (in years)	Kinsey Ratings		DSM
				Fantasy	Behavior	
135	2009-03-09	12.06	23.98	(6)	—	+
136	2010-01-07	6.76	19.50	—	—	+
137	2009-06-08	11.91	23.29		—	-
138	2009-03-11	8.79	18.19	—	—	+
139	2009-02-02	11.90	21.17	(6)	—	-

Note. For Kinsey ratings (last 12 months), 0 = exclusively heterosexual in relation to birth sex and 6 = exclusively homosexual in relation to birth sex. A dash in the Kinsey columns indicate that data were not available. A bracketed score in the Kinsey Fantasy column indicates that the participant did not complete a full sexual orientation interview but sufficient data were available to inform a Kinsey rating. In the DSM column, a plus sign indicates the participant meet full *DSM-III*, *DSM-III-R*, or *DSM-IV* criteria for GID at the childhood assessment. A minus sign indicates the participant was subthreshold for the diagnosis of GID.

^aSome participants were assessed at more than one follow-up points. In these cases, data from the most recent assessment were used.

Appendix L

Diagnostic Interview for Children and Adolescents or Diagnostic Interview Schedule

Diagnoses at Follow-up

Diagnostic Interview for Children and Adolescents Diagnoses at Follow-up

ID	Diagnosis(es)	No. of Diagnoses	Clinical Comments
1	None	0	
2	None	0	
3	Adjustment Disorder with Depressed Mood	1	
4	None	0	
5	None	0	
6	None	0	
7	None	0	
8	None	0	
9	Conduct, Non-Aggressive Alcohol Abuse	2	
10	None	0	
11	None	0	
12	None	0	
13	None	0	
14	None	0	
15	None	0	
16	Adjustment Disorder with Depressed mood	1	
17	Conduct, Non-aggressive Adjustment Disorder with Depressed Mood	2	

Diagnostic Interview for Children and Adolescents Diagnoses at Follow-up

ID	Diagnosis(es)	No. of Diagnoses	Clinical Comments
18	None	0	
19	None	0	
20	Conduct, Non-Aggressive	1	
21	None	0	
22	None	0	
23	Conduct, Non-Aggressive Adjustment Disorder with Depressed Mood	2	
24	None	0	
25	None	0	
26	None	0	
27	None	0	
28	Overanxious Disorder	1	
29	Conduct, Aggressive	1	
30	None	0	
31	Conduct, Non-Aggressive Adjustment Disorder with Depressed Mood	2	Multiple suicide attempts
32	None	0	
33	None	0	
34	None	0	

Diagnostic Interview for Children and Adolescents Diagnoses at Follow-up

ID	Diagnosis(es)	No. of Diagnoses	Clinical Comments
35	None	0	
36	None	0	
37	Conduct, Aggressive Major Depression	2	1 suicide attempt (prescription medication)
38	Overanxious Disorder	1	
39	Marijuana Abuse Adjustment Disorder with Depressed Mood	2	2 suicide attempts
40	Adjustment Disorder with Depressed Mood Overanxious Disorder	2	Medications: Prozac and Zoloft
41	Adjustment Disorder with Depressed Mood	1	2 suicide attempts
42	Conduct, Non-Aggressive	1	
43	None	0	Sub-threshold for Major Depression
44	Overanxious Disorder	1	Sub-threshold for Major Depression
45	Conduct, Non-Aggressive Conduct, Aggressive Alcohol Abuse Marijuana Abuse Other Drug Abuse (Cocaine) Adjustment Disorder with Depressed Mood Overanxious Disorder	7	Medication: Paxil, Zanax

Diagnostic Interview for Children and Adolescents Diagnoses at Follow-up

ID	Diagnosis(es)	No. of Diagnoses	Clinical Comments
46	Adjustment Disorder with Depressed Mood	1	
47	Oppositional Disorder Adjustment Disorder with Depressed Mood	2	Sub-threshold for Alcohol Abuse; was on anti-depressant medication; 2 suicide attempts
48	Oppositional Disorder	1	
49	Adjustment Disorder with Depressed Mood Overanxious Disorder	2	
50	None	0	
51	Major Depression Overanxious Disorder	2	Medication: Paxil
52	Conduct, Non-Aggressive Alcohol Abuse Marijuana Abuse Other Drug Abuse (Ketamine, Ecstasy) Other Drug Dependence (Ketamine, Ecstasy) Major Depression Overanxious Disorder	7	
53	None	0	
54	None	0	
55	Oppositional Defiant Disorder	1	Sub-threshold for major depression
56	None	0	

Diagnostic Interview for Children and Adolescents Diagnoses at Follow-up

ID	Diagnosis(es)	No. of Diagnoses	Clinical Comments
57	Conduct, Aggressive Conduct, Non-Aggressive Other Drug Abuse (Ecstasy) Adjustment Disorder with Depressed Mood	4	Medications: Wellbutrin and Celexa; 1 suicide attempt
58	Overanxious Disorder	1	Was on Prozac
59	Alcohol Abuse Alcohol Dependence Marijuana Abuse Other Drug Abuse (Hallucinogens) Other Drug Dependence (Hallucinogens) Adjustment Disorder with Depressed Mood Overanxious Disorder	7	1 suicide attempt
60	Conduct, Non-Aggressive	1	
61	None	0	
62	Major Depression Overanxious Disorder	2	Medication: Zoloft
63	Oppositional Disorder Marijuana Abuse	2	Prozac
64	None	0	

Diagnostic Interview Schedule Diagnoses at Follow-up

ID	Diagnosis(es)	No. of Diagnoses	Clinical Comments
1	None	0	
2	None	0	
3	None	0	Medication: Effexor
4	None	0	
5	None	0	On medication for ADHD
6	None	0	Sub-threshold for Drug Abuse (Marijuana, Cocaine) and Drug Dependence
7	None	0	
8	Drug Dependence (Amphetamines)	1	
9	Alcohol Abuse	1	
10	Alcohol Abuse	1	
11	Major Depression, Single Episode	1	
12	Alcohol Abuse	1	Sub-threshold for Major Depression
13	Major Depression, Recurrent	1	
14	Major Depression, Recurrent	1	1 suicide attempt
15	Simple Phobia	1	Sub-threshold for Drug Abuse and Dependence
16	Major Depression, Recurrent	1	Sub-threshold for Bulimia
17	Major Depression, Single Episode	1	Sub-threshold for Drug Abuse (Marijuana)
18	Major Depression, Recurrent Alcohol Dependence	2	

Diagnostic Interview Schedule Diagnoses at Follow-up

ID	Diagnosis(es)	No. of Diagnoses	Clinical Comments
19	Alcohol Abuse Alcohol Dependence	2	Sub-threshold for Major Depression; attempted suicide
20	Obsessive Compulsive Disorder Simple Phobia (exclusion not met)	2	
21	Major Depression, Single Episode Alcohol Abuse	2	
22	Social Phobia Generalized Anxiety	2	
23	Major Depression, Single Episode Generalized Anxiety (exclusion not met)	2	
24	Dysthymic Disorder Alcohol Abuse Alcohol Dependence	3	
25	Major Depression, Single Episode Social Phobia (exclusion not met) Panic Disorder (exclusion not met)	3	Sub-threshold for Alcohol Dependence and Drug Abuse (Marijuana); hypomanic episodes in preceding year; taking Celexa
26	Major Depression, Recurrent Obsessive Compulsive Disorder (exclusion not met) Social Phobia (exclusion not met) Generalized Anxiety Disorder (exclusion not met)	4	On medication for anxiety
27	Major Depression, Recurrent Alcohol Abuse Social Phobia (exclusion not met) Panic Disorder (exclusion not met)	4	Sub-threshold for Drug Dependence
28	Major Depression, Recurrent Alcohol Abuse Alcohol Dependence Generalized Anxiety (exclusion not met)	4	Sub-threshold for Drug Dependence (Marijuana)

Diagnostic Interview Schedule Diagnoses at Follow-up

ID	Diagnosis(es)	No. of Diagnoses	Clinical Comments
29	Major Depression, Recurrent Alcohol Abuse Drug Abuse (Marijuana, Ecstasy, Cocaine) Drug Dependence (Marijuana, Ecstasy, Cocaine)	4	Took antidepressants; 1 suicide attempt
30	Major Depression (Recurrent) Agoraphobia (exclusion not met) Social Phobia (exclusion not met) Generalized Anxiety (exclusion not met)	4	1 suicide attempt
31	Major Depression, Recurrent Simple Phobia Agoraphobia (exclusion not met) Social Phobia (exclusion not met)	4	On antidepressants
32	Mania (Bipolar) Drug Abuse (Cocaine, Opiates) Drug Dependence (Cocaine, Opiates) Simple Phobia Generalized Anxiety	5	
33	Major Depression, Recurrent Drug Abuse (Marijuana) Drug Dependence (Marijuana) Bulimia Generalized anxiety (exclusion not met)	5	
34	Major Depression, Recurrent Alcohol Abuse Alcohol Dependence Dysthymic Disorder (exclusion not met) Generalized Anxiety (exclusion not met)	5	
35	Major Depression, Recurrent Alcohol Abuse Drug Dependence (Marijuana) Obsessive Compulsive Disorder (exclusion not met) Generalized Anxiety (exclusion not met)	5	Took antidepressants
36	Major Depression, Recurrent Alcohol Abuse Drug Abuse (Marijuana, Cocaine, Ecstasy) Drug Dependence (Marijuana, Cocaine, Ecstasy) Simple Phobia	5	Medications: Celexa, Ritalin; arrested and then hospitalized once for uttering death threats to mother

Diagnostic Interview Schedule Diagnoses at Follow-up

ID	Diagnosis(es)	No. of Diagnoses	Clinical Comments
37	Major Depression, Recurrent Alcohol Abuse Alcohol Dependence Drug Abuse (Marijuana, Cocaine, Amphetamines) Drug Dependence (Marijuana, Cocaine, Amphetamines)	5	
38	Major Depression, Single Episode Dysthymic Disorder (exclusion not met) Social Phobia (exclusion not met) Agoraphobia with Panic Attacks (exclusion not met) Generalized Anxiety (exclusion not met)	5	1 suicide attempt
39	Major Depression, Recurrent Simple Phobia Agoraphobia (exclusion not met) Social Phobia (exclusion not met) Generalized Anxiety (exclusion not met)	5	
40	Major Depression, Recurrent Drug Abuse (Marijuana, Ecstasy, Ketamine) Drug Dependence (Marijuana, Ecstasy) Simple Phobia Social Phobia (exclusion not met) Agoraphobia with Panic Attacks (exclusion not met)	6	Was on anti-depressant medication (Zoloft); 1 suicide attempt
41	Major Depression, Recurrent Drug Abuse (Marijuana) Drug Dependence (Marijuana) Panic Disorder (exclusion not met) Generalized Anxiety (exclusion not met) Bulimia (exclusion not met)	6	Medication: Cipralex
42	Mania (Bipolar) Alcohol Abuse Bulimia Dysthymic Disorder (exclusion not met) Obsessive-Compulsive Disorder (exclusion not met) Agoraphobia with Panic Attacks (exclusion not met) Generalized Anxiety (exclusion not met)	7	Sub-threshold for Drug Abuse and Dependence; attempted suicide

Diagnostic Interview Schedule Diagnoses at Follow-up

ID	Diagnosis(es)	No. of Diagnoses	Clinical Comments
43	Major Depression, Recurrent Alcohol Abuse Alcohol Dependence Dysthymic Disorder (exclusion not met) Obsessive Compulsive Disorder (exclusion not met) Simple Phobia (exclusion not met) Panic Disorder (exclusion not met) Generalized Anxiety (exclusion not met)	8	Medications: Lorazepam, Paxil, Wellbutrin
44	Major Depression, Recurrent Alcohol Abuse Drug Abuse (Ketamine) Drug Dependence (Cocaine, Ketamine) Simple Phobia Bulimia Dysthymic Disorder (exclusion not met) Panic Disorder (exclusion not met) Generalized Anxiety (exclusion not met)	9	Medication: Effexor; diagnosed with AIDS

Appendix M

Gender Identity and Sexual Orientation Outcomes in Follow-up Studies of Boys with GID

Gender Identity and Sexual Orientation in other Follow-up Studies of Boys with GID

	Persistence of Gender Dysphoria (%)	Sexual Orientation in Fantasy		Sexual Orientation in Behavior	
		Heterosexual (%)	Homosexual/Bisexual (%)	Heterosexual (%)	Homosexual/Bisexual (%)
Six studies summarized by Zucker & Bradley (1995) ^a	9.1 (n = 5)	-	-	-	-
Green (1987)	2.3 (n = 1)	25 (n = 11)	75 (n = 33)	20 (n = 6)	80 (n = 24)
Wallien & Cohen-Kettenis (2008)	20.3% or 30% ^b (n = 12)	19 ^c (n = 4)	81 (n = 17)	21 ^d (n = 4)	79 (n = 15)
Singh (2012) (Present Study)	12.2 (n = 17)	33.3 (n = 43)	63.6 (n = 82)	26.9 (n=29)	47.2 (n = 51)

^aThe sexual orientation results for these six studies (taken collectively due to the same sample size of the individual studies) are not reported here because it was unclear whether sexual orientation was measured according to fantasy or behavior.

^bThis percentage reflects the persistence rate for only the males in the study. Two rates were obtained depending on the sample used to calculate the persistence rate. The conservative rate of 30% was obtained when persistence was calculated using only those boys who were successfully traced at follow-up were included in the study. The persistence rate of 20.3% was obtained using a liberal criterion whereby the boys who could not be traced and who were assumed to be desisters were included in the study.

^cData on sexual orientation in fantasy were available for 21 of the 40 males who completed the follow-up assessment.

^dData on sexual orientation in behavior were available for 19 of the 40 males who completed the follow-up assessment.

EXHIBIT E

A Follow-Up Study of Girls With Gender Identity Disorder

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This study provided information on the natural histories of 25 girls with gender identity disorder (GID). Standardized assessment data in childhood (mean age, 8.88 years; range, 3–12 years) and at follow-up (mean age, 23.24 years; range, 15–36 years) were used to evaluate gender identity and sexual orientation. At the assessment in childhood, 60% of the girls met the *Diagnostic and Statistical Manual of Mental Disorders* criteria for GID, and 40% were subthreshold for the diagnosis. At follow-up, 3 participants (12%) were judged to have GID or gender dysphoria. Regarding sexual orientation, 8 participants (32%) were classified as bisexual/homosexual in fantasy, and 6 (24%) were classified as bisexual/homosexual in behavior. The remaining participants were classified as either heterosexual or asexual. The rates of GID persistence and bisexual/homosexual sexual orientation were substantially higher than base rates in the general female population derived from epidemiological or survey studies. There was some evidence of a “dosage” effect, with girls who were more cross-sex typed in their childhood behavior more likely to be gender dysphoric at follow-up and more likely to have been classified as bisexual/homosexual in behavior (but not in fantasy).

Keywords: gender identity disorder, gender identity, sexual orientation, girls, follow-up

Research on normative (or typical) gender development has documented various behavioral domains in which children show, on average, significant sex differences: gender identity self-labeling, sex-of-playmate preference, toy and activity interests, roles in fantasy play, parental rehearsal play, and so on (for a review, see Ruble, Martin, & Berenbaum, 2006; Zucker, 2005c). The determinants of this between-sex variation in sex-typed behavior have long been deemed by developmentalists to have important implications for other aspects of psychosocial development, such as interpersonal relational styles (e.g., Maccoby, 1998), cognitive skills (e.g., Liss, 1983), and vocational interests (e.g., Lippa, 1998), for which there are also significant sex differences.

As noted by Lippa (2002), determining within-sex individual differences in gender-related behavior is another strategy used to study variations with regard to other aspects of development (see, e.g., Barrett & White, 2002; Khuri & Ruble, 2006). In the present study, we used this approach to examine the relation, if any, between sex-typed behavior patterns in childhood, including gen-

der identity, and subsequent gender identity and sexual orientation in late adolescent girls and young adult women.

Several lines of evidence suggest that there are empirical reasons to posit a link between sex-typed behavior in childhood and later gender identity and sexual orientation. Like sex-typed behavior in childhood, gender identity and sexual orientation in adulthood are also sex dimorphic: Most women have a “female” gender identity (the subjective sense of self as a woman) and are sexually attracted to men, whereas most men have a “male” gender identity and are sexually attracted to women. Indeed, gender identity and sexual orientation may be the two behavioral traits that most strongly differentiate women from men (cf. Hyde, 2005). Using a self-report questionnaire designed to measure gender identity dimensionally in adolescents and adults, for example, Deogracias et al. (2007) obtained a between-sex effect size, using Cohen’s *d*, of 13.24.

Over the past several decades, the empirical literature has relied on two methods, namely, retrospective and prospective designs using targeted samples, to examine the relation between sex-typed behavior in childhood and subsequent gender identity and sexual orientation in adulthood. Retrospective designs have studied adults with known variation in their gender identity and/or sexual orientation. For example, adults who meet the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* criteria for gender identity disorder (GID; also known as transsexualism) recall engaging in more cross-gender-typed behavior in childhood than do adults without GID (e.g., Blanchard & Freund, 1983; Doorn, Poortinga, & Verschoor, 1994; Ehrhardt, Grisanti, & McCauley, 1979; Freund, Langevin, Satterberg, & Steiner, 1977; see also Bartlett & Vasey, 2006).

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The largest body of retrospective research pertains to the within-sex association between sex-typed behavior in childhood and sexual orientation in adulthood. Bailey and Zucker (1995) performed a meta-analysis of 41 retrospective studies that made a quantitative comparison between heterosexual and homosexual same-sex adults using some measure of childhood sex-typed behavior. These studies yielded 48 independent effect sizes: 32 compared heterosexual and homosexual men, and 16 compared heterosexual and homosexual women. Using Cohen's *d*, Bailey and Zucker found that there were substantial differences in patterns of recalled childhood sex-typed behavior between heterosexual and homosexual adults. On average, both homosexual men and women recalled more cross-sex-typed behavior in childhood than did their heterosexual counterparts (respective *ds* were 1.31 and 0.96). Subsequent studies have, with no exception, continued to replicate these findings (summarized in Zucker et al., 2006).

There are, of course, both methodological and interpretive problems with retrospective designs (for an overview, see Hardt & Rutter, 2004). In a targeted sample of adults with GID (invariably recruited from specialized gender identity clinics), it is possible that the association with cross-sex-typed behavior is magnified because not all individuals with pervasive cross-gender behavior in childhood end up seeking out medically assisted gender change in adulthood (e.g., because their earlier gender dysphoria had desisted). In the studies comparing the recollections of heterosexual and homosexual adults, in which there is less of a sampling bias problem, the most common criticism has pertained to memory distortion or selective recall. For example, it has been argued that the greater recollection of cross-gender behavior during childhood by homosexual than by heterosexual adults is linked to the widespread "master narrative" in Western culture that presupposes that "gender inversion" is linked to homosexual sexual orientation (see, e.g., Cohler & Galatzer-Levy, 2000; Gottschalk, 2003; Hegarty, 1999; Kite & Deaux, 1987). As a result, it has been claimed that the sex-typed behavior–sexual orientation association is nothing more than participants recalling behaviors that adhere to cultural stereotypes and expectations. Although there is evidence that speaks against this retrospective distortion hypothesis (summarized in Bailey & Zucker, 1995; Zucker, 2005a, in press; Zucker et al., 2006), there is general agreement that the retrospective data should be confirmed (or disconfirmed) with prospective designs.

One prospective approach has been to target a sample of children presumed to have moderate-to-pervasive cross-gender behavior. In one line of research, sampling consisted of ad-recruited girls with parent-nominated "tomboyish" behavior, along with measures of sex-typed behavior administered to the girls themselves (e.g., Bailey, Bechtold, & Berenbaum, 2002; Berenbaum & Bailey, 2003; Green, Williams, & Goodman, 1982), who were compared to girls unselected for their gender behavior. Neither research team has, as of yet, reported on longer term linkages.

A second strategy has been to study children referred to specialized gender identity clinics because there is concern about their cross-gender behavior and gender identity status (e.g., on the part of parents, mental health professionals, teachers, etc.). Over the years, several research teams have studied such children, and overviews may be found in the work of Green (1987), Zucker and Bradley (1995), and Cohen-Kettenis and Pfäfflin (2003).

In one study, Green (1987) assessed the gender identity and sexual orientation of 44 behaviorally feminine boys and 30 control

boys who were at a follow-up mean age of 18.9 years (range, 14–24 years) and who had initially been evaluated at a mean age of 7.1 years (range, 4–12 years). Of the 44 behaviorally feminine boys, only 1 youth, at the age of 18 years, was gender dysphoric to the extent of considering sex-reassignment surgery. None of the other boys were reported to have gender identity problems at follow-up. Sexual orientation in fantasy and behavior was assessed by means of a semistructured, face-to-face interview. Kinsey ratings were made on a 7-point continuum, ranging from exclusive heterosexuality (a Kinsey "0") to exclusive homosexuality (a Kinsey "6"; Kinsey, Pomeroy, & Martin, 1948). Depending on the measure (fantasy or behavior), 75%–80% of the previously behaviorally feminine boys were either bisexual or homosexual (Kinsey ratings between 2 and 6) at follow-up versus 0%–4% of the control boys.

Data from seven other follow-up reports on a total of 82 behaviorally feminine boys have been summarized in detail elsewhere (Zucker, 2005b; Zucker & Bradley, 1995, pp. 285–286, 290–297). Similar to Green's (1987) case-control study, these studies also identified an elevated rate of either a bisexual or homosexual sexual orientation (52.4%). In contrast to Green's (1987) study, however, the other studies found the rate of GID persistence was higher, with rates ranging from 12% to 20%.

From these prospective studies of behaviorally feminine boys, two conclusions might be drawn: (a) The rate of persistent gender dysphoria was modest but arguably higher than one estimated base rate for gender dysphoria in the general population of biological males: 1 in 11,000 men (Bakker, van Kesteren, Gooren, & Bezeemer, 1993), and (b) the rate of a later bisexual or homosexual sexual orientation was notably higher than the known base rates for a bisexual or homosexual sexual orientation in the general population of biological males (see, e.g., Laumann, Gagnon, Michael, & Michaels, 1994). Thus, for sexual orientation, there appears to be a reasonable convergence between prospective and retrospective studies but, for gender identity, there is more divergence: Many boys with pervasive cross-gender behavior and co-occurring gender dysphoria do not show persistent gender dysphoria by late adolescence or young adulthood, which is at some variance from the recollections of most gender-dysphoric adolescent boys and adult men.

Over the years, it has been noted that little is known about the longer term psychosexual outcome of girls referred to specialized gender identity clinics (Peplau & Huppert, in press; Peplau, Spalding, Conley, & Veniegas, 1999). In part, this has been a function of the fact that boys are much more likely than girls to be referred to gender identity clinics: 5.75:1 in one clinic and 3.07:1 in another (see Cohen-Kettenis, Owen, Kaijser, Bradley, & Zucker, 2003; Cohen-Kettenis et al., 2006). The present study attempted to fill this gap by providing, to our knowledge, the first systematic follow-up report of clinic-referred girls with GID with regard to gender identity and sexual orientation.

Method

Participants

Between 1975 and 2004, 71 girls (age range, 3–12 years) were referred for assessment to the Gender Identity Service, Child, Youth, and Family Program at the Centre for Addiction and

Mental Health in Toronto, Ontario, Canada. To participate in the follow-up study, patients had to be at least 17 years of age. Using this age cutoff, we identified 37 eligible girls, of whom 30 were contacted for participation. Of the remaining 7 girls, 3 could not be traced through previous addresses, registrars, and personal contacts (e.g., the patient and/or their family had moved and a current telephone number, mailing address, or e-mail address could not be identified), and 4 were not available to participate within the time requirements of the study.

Initial telephone contact was first made with the parents or legal guardians because participants were minors at the time of assessment and some may have had no recollection of their clinic attendance.¹ Of the 30 clients contacted, 25 (83.3%) agreed to participate; 24 came into the clinic for testing, and 1 participant completed a telephone interview because she was too anxious to travel to the clinic. Of the remaining 5 girls, 4 of the girls' parents or guardians (e.g., the Children's Aid Society) were unwilling to provide contact information for their children. One individual declined to participate.

The demographic characteristics of the participants in childhood and at follow-up are shown in Table 1. The GID diagnosis in childhood was based on the *DSM* (3rd ed. [*DSM-III*]; 3rd ed., rev. [*DSM-III-R*]; or 4th ed. [*DSM-IV*]; American Psychiatric Association [APA], 1980, 1987, and 1994, respectively) criteria applicable at the time of assessment. Fifteen girls (60%) met complete

DSM criteria for GID in childhood. The remaining 40% were subthreshold for a *DSM* diagnosis of GID, but all had some indicators of GID, and some would have met the complete *DSM* criteria at some point in their lives prior to their assessment in childhood.

Four of the girls in the follow-up sample were born with a disorder of sex development (DSD; 2 had cloacal exstrophy, 1 had congenital micropenis syndrome of unknown etiology, and 1 had mixed gonadal dysgenesis; Hughes, Houk, Ahmed, Lee, & Lawson Wilkins Pediatric Endocrine Society/European Society for Paediatric Endocrinology Consensus Group, 2006). Three of the nonparticipants also had a DSD (partial androgen insensitivity syndrome, congenital adrenal hyperplasia, or true hermaphroditism). There are arguments for and against the inclusion of the 4 girls with a DSD in this sample (see, e.g., Meyer-Bahlburg, 1994). A female gender assignment was made for all 4 girls almost immediately after birth. Also in early infancy, the 4 girls were gonadectomized and had surgical feminization of their external genitalia. Like the somatically intact girls, the 4 girls were referred for concern about their gender development in relation to their assigned gender. On the one hand, as noted by Meyer-Bahlburg (2005), "there is every reason to assume that the processes and psychosocial factors involved in normative gender development also contribute to development of all aspects of gender. . . in persons with intersexuality" (p. 434). On the other hand, as also noted by Meyer-Bahlburg (2005), "additional factors. . . may come into play in [such persons]. . . particularly the awareness of an atypical biological condition and medical history" (pp. 434–435). As noted in Table 3, only 1 of these girls met the complete Point A and Point B *DSM* criteria for GID, and the other 3 were subthreshold.

Table 1
Demographic Characteristics (N = 25)

Characteristic	<i>M</i>	<i>SD</i>	Range	%
From childhood				
Age (in years)	8.88	3.10	3.17–12.95	
Year of assessment	1989.36	7.02	1977–2002	
IQ ^{a, b}	105.17	21.73	57–144	
Social class ^c	35.72	14.40	8–66	
Marital status ^d				
Two-parent family				60.0
Other				40.0
Caucasian				80.0
At follow-up				
Age (in years) ^e	23.24	5.82	15.44–36.58	
Year of birth	1980.52	6.06	1968–1989	
Interval (in years) ^f	14.34	7.03	2.99–27.12	
IQ ^{b, g}	10.20	2.71	5.00–15.75	

^a Full-scale IQ was obtained with age-appropriate Wechsler intelligence scales (the Wechsler Preschool and Primary Scale of Intelligence—Third Edition [Wechsler, 2002], the Wechsler Intelligence Scale for Children—Revised [Wechsler, 1974], and the Wechsler Intelligence Scale for Children—Third Edition [Wechsler, 1991]). One participant was administered the Stanford-Binet Intelligence Scale (Thorndike, Hagen, & Sattler, 1986). ^b IQ scores at assessment and follow-up were not available for 1 participant. ^c For social class, Hollingshead's (1975) Four Factor Index of Social Status was used. The absolute range was 8–66. ^d For marital status, the category "Other" included the following family constellations: single parent, separated, divorced, living with relatives, or in the care of the Children's Aid Society. ^e One participant (who was 15.44 years of age) was below the lower bound age cutoff of 17 years but was included in the study because her guardian had contacted the clinic for issues unrelated to gender identity status. ^f Interval denotes the time between childhood assessment and follow-up assessment. ^g Composite IQ = (Vocabulary + Comprehension + Block Design + Object Assembly subscale scores)/4. The absolute range was 1–19.

Procedure

All participants were evaluated on a single day. Below, we provide information on the measures used in this report (for other measures, including parent and self-ratings of behavior problems, psychiatric diagnoses, and experiences of stigma, see Drummond, 2006). All of the participants provided written informed consent prior to their involvement in the follow-up assessment and were provided a stipend for their participation and reimbursement for travel expenses. The study was approved by the Institutional Review Boards at the Centre for Addiction and Mental Health and the University of Toronto.

¹ It is beyond the scope of this report to describe the types of therapies (as well as their frequency and duration) that the girls and/or their parents may have received between the assessment in childhood and the follow-up (e.g., by a therapist within the Gender Identity Service at the Centre for Addiction and Mental Health or in the community). From the participants' clinic files, 13 of the 25 girls had at least some contact with our clinic during the interval between assessment and follow-up (e.g., as therapy clients or for a reassessment). Of the 25 girls and/or their parents, 18 had been in some type of therapy or counseling during the interval between assessment and follow-up; of these, 5 were patients of staff within the Gender Identity Service, and the remainder were seen by a professional in the community.

Measures

Childhood Assessment

Cognitive functioning. IQ was assessed with the Wechsler Adult Intelligence Scale—Third Edition (Wechsler, 1997) or the Wechsler Intelligence Scale for Children—Third Edition (Wechsler, 1991) and, for one participant, with the Stanford-Binet Intelligence Scale (Thorndike, Hagen, & Sattler, 1986).

Sex-typed behavior. Five child informant and three parent informant measures were used to assess the participants' sex-typed behavior in childhood: (a) the Draw-a-Person test (Zucker, Finegan, Doering, & Bradley, 1983); (b) a free-play task (Zucker, Doering, Bradley, & Finegan, 1982); (c) the Playmate and Playstyle Preferences Structured Interview (Fridell, Owen-Anderson, Johnson, Bradley, & Zucker, 2006); (d) sex-typed responses on the Rorschach test (Zucker, Lozinski, Bradley, & Doering, 1992); (e) the Gender Identity Interview (Zucker et al., 1993); (f) the Gender Identity Questionnaire for Children (Johnson et al., 2004); (g) a measure of activity level/extraversion (Zucker & Bradley, 1995); and (h) the Games Inventory (Bates & Bentler, 1973). These child and parent informant measures all had established discriminant validity, that is, they significantly differentiated the clinic girls referred for gender identity concerns from control girls (for a review, see Zucker, 2005c; Zucker & Bradley, 1995). A Childhood Sex-Typed Behavior Composite was computed for each participant by averaging the *z*-scores for these measures (which yielded a total of 11 indices), as well as the GID *DSM* diagnosis (1 = *threshold*, 2 = *subthreshold*) in childhood. Data from the total sample of participants and nonparticipants (*N* = 37) were used. Because of missing data, the mean number of indices/participant was 9.16 (*SD* = 2.30).

Follow-Up Assessment

Cognitive functioning. Four subtests (Vocabulary, Comprehension, Block Design, and Object Assembly) of the Wechsler Adult Intelligence Scale—Third Edition or the Wechsler Intelligence Scale for Children—Third Edition were administered. The standard scores from the subtests were averaged to form an IQ score for cognitive functioning.

Recalled childhood gender identity and gender role behavior. Participants completed the Recalled Childhood Gender Identity/Gender Role Questionnaire (RCGI; Zucker et al., 2006). This questionnaire consists of 23 items pertaining to various aspects of sex-typed behavior, as well as to the relative closeness to the mother and father during childhood. Individual items were rated on a 5-point response scale. Each participant was instructed to make ratings for her behavior as a child ("between the years 0 to 12"). Factor analysis identified two factors, accounting for 37.4% and 7.8% of the variance, respectively (all factor loadings $\geq .40$). Factor 1 consisted of 18 items that pertained to childhood gender role and gender identity, and Factor 2 consisted of three items that pertained to parent-child relations (relative closeness to one's mother versus one's father). Information on normative sex differences and discriminant validity was reported in Zucker et al. (2006). For the present study, the mean Factor 1 score was computed for each participant.

Concurrent gender identity. During an audiotaped interview, each participant was asked to describe her current feelings about

being female and then to describe positive and negative aspects about her gender status. The examiner also asked semistructured gender identity questions from the adolescent and adult GID criteria outlined in the *DSM-IV-TR* (APA, 2000). The interviewer asked four questions related to the Point A criteria (e.g., the stated desire to be a man, the desire to live or to be treated as a man) and six questions from the Point B criteria (e.g., a preoccupation with getting rid of breasts or genitalia). Participants were asked to respond according to the last 12 months with *No*, *Yes*, or *Sometimes*. Participants who answered *Yes* or *Sometimes* for one or more of the questions from both Point A and B criteria were classified as displaying persistent gender dysphoria.

The female version of the Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults (GIDQ-AA; Deogracias et al., 2007) was also completed. This 27-item questionnaire measures gender identity and gender dysphoria in adolescents or adults. Item content was based on prior measures, expert panels, and clinical experience. Each item was rated on a 5-point response scale ranging from *Never* to *Always* based on a time frame of the past 12 months. Item examples include the following: "In the past 12 months, have you felt unhappy about being a woman?" and "In the past 12 months, have you wished to have an operation to change your body into a man's (e.g., to have your breasts removed or to have a penis made)?" Factor analysis identified a strong one-factor solution that accounted for 61.3% of the variance. All 27 items had factor loadings $\geq .30$ (median, .86; range, .34–.96). Psychometric evidence for discriminant validity and clinical utility can be found in Deogracias et al. (2007). Participants' GIDQ-AA total scores were calculated by summing scores on the completed items and dividing by the number of marked responses.

Sexual orientation in fantasy. Each participant's sexual orientation in fantasy was assessed with specific questions during an audiotaped face-to-face interview and the self-report Erotic Response and Orientation Scale (EROS; Storms, 1980). Questions posed in the interview addressed four types of sexual fantasy: (a) crushes on other people, (b) sexual arousal to visual stimuli (e.g., to strangers, acquaintances, partners, and individuals presented in the media [video, movies, magazines, the internet]), (c) sexual content of night dreams, and (d) sexual content of masturbation fantasies. Using the Kinsey scale criteria, the interviewer assigned ratings that ranged from 0 (*exclusively heterosexual*) to 6 (*exclusively homosexual*) for each parameter. A dummy score of 7 denoted that the participant did not experience or report any fantasies. A global fantasy score was derived on the basis of ratings from the four questions. In the present study, only ratings for the last 12 months are reported.

During the interview, participants were not asked directly about the gender of the person or persons who elicited sexual arousal, thus allowing time for the participant to provide this information spontaneously. Directed questions were asked only if the participant did not volunteer specific information about same-sex or opposite-sex partners. This approach was used so that, by the end of the interview, the participant provided information about sexual arousal to both same-sex and opposite-sex individuals.

The EROS is a 16-item self-report measure assessing sexual orientation in fantasy over the past 12 months. Half of the questions pertained to heterosexual fantasy (e.g., "How often have you had any sexual feelings (even the slightest) while looking at a man?") and the other half pertained to homosexual fantasy (e.g.,

“How often have you had any sexual feelings (even the slightest) while looking at a woman?”). Each item was rated on a 5-point scale for frequency of occurrence, ranging from “none” to “almost every day.” Mean homoerotic and heteroerotic fantasy scores were derived for each participant. Previous use of the EROS has shown good evidence of discriminant validity (Storms, 1980; Zucker et al., 1996).

Sexual orientation in behavior. Each participant’s sexual orientation in behavior was assessed with specific questions during the face-to-face interview and with a modified version of the Sexual History Questionnaire (SHQ; Langevin, 1985). In the interview, questions asked about five types of sexual behavior: (a) dating; (b) holding hands in a romantic manner; (c) kissing; (d) genital fondling or being touched on the breasts (or, in cases of same-sex sexual behavior, touching another woman’s breasts); and (e) penile–vaginal intercourse, anal intercourse, or the use of dildos. Kinsey ratings for behavior for the past 12 months were made in the same manner as fantasy ratings.

The modified SHQ consisted of 20 questions. Ten questions pertained to heterosexual experiences (e.g., “How many men have you kissed on the lips in a romantic way?”), and 10 questions pertained to homosexual experiences (e.g., “How many women have you kissed on the lips in a romantic way?”). Each item was rated, for the 12 month period prior to the follow-up assessment, on a 5-point scale for frequency of occurrence, ranging from none to 11 or more. Mean total scores for heterosexual and homosexual experiences were derived.

Sexual identity self-labeling. Participants were asked to provide a label for their current sexual identity and were offered the following options: (a) “straight” or “heterosexual”; (b) “lesbian,” “homosexual,” or “queer”; (c) “bisexual”; (d) “asexual”; or (e) “other.”

Social desirability. Social desirability can threaten the validity of self-report scales when respondents seek social approval or try to represent themselves in a favorable manner (King & Brunner, 2000). Participants ≥ 18 years of age completed the Marlowe–Crowne Social Desirability Scale (M–C SDS; Crowne & Marlowe, 1960), which consists of 33 true–false items. The scale consists of 18 culturally acceptable but unlikely statements keyed in the true direction and 15 socially undesirable but probable statements keyed in the false direction for a maximum possible score of 33. Participants under 18 years of age completed a shorter version of the M–C SDS (Strahan & Gerbasi, 1972). This scale consists of 12 culturally acceptable but improbable statements keyed in the true direction and 8 socially undesirable but probable statements keyed in the false direction for a maximum possible score of 20. Several studies have found that the M–C SDS is a reliable and valid measure (Crowne & Marlowe, 1960; Holden & Fekken, 1989; Silverthorn & Gekoski, 1995).

Results

Participants Versus Nonparticipants

A preliminary analysis compared the assessment information from childhood of the 25 girls who participated in the study with that of the 12 girls who did not participate. There were no significant differences between the participants and nonparticipants on any of these variables (data not shown).² At least by these mea-

Table 2

Mean Factor 1 Score on the Recalled Childhood Gender Identity/Gender Role Questionnaire (Zucker et al., 2006)

Group	<i>M</i>	<i>SD</i>	<i>d</i>	<i>n</i>
Total sample	2.57	.67		20
(Female university students)	(3.43)	(.54)		(100)
(Mothers of boys with GID)	(3.80)	(.54)		(230)
(Mothers of control boys)	(3.72)	(.34)		(13)
(Mothers of nonreferred boys)	(3.77)	(.39)		(24)
(Sisters/female cousins of women with CAH)	(3.70)	(.43)		(15)
Childhood diagnosis				
GID: Threshold	2.48	.66	.32	11
GID: Subthreshold	2.70	.69		9

Note. Absolute range is 1.00–5.00. A lower score indicates more recalled atypical gender identity and gender role behavior. Groups and values in parentheses are from Zucker et al. (2006). GID = gender identity disorder; CAH = congenital adrenal hyperplasia.

sures, it appears that the participants were representative of the total pool of available patients and thus did not constitute a markedly biased sample at follow-up.

Sex-Typed Behavior in Childhood

Table 2 shows the mean RCGI Factor 1 score, which pertained to the participants’ recollections of their sex-typed behavior from childhood. This mean score can be compared with the scores of several samples of women, unselected for their gender identity or sexual orientation, reported on in Zucker et al. (2006) and also shown in Table 2. By comparing the mean factor score with the scores from the other samples (mean range, 3.43–3.80), we see it is apparent that the women in this study recalled relatively more cross-gender behavior in childhood ($M = 2.57$, $SD = .67$).

Table 2 also shows the mean RCGI Factor 1 score of the participants as a function of *DSM* diagnostic status in childhood. Although the threshold participants recalled, on average, more cross-gender behavior in childhood than the subthreshold participants, the difference was not significant, $t(18) < 1$; the effect size (Cohen’s d) of .32 would be considered small. We also examined the z -composite for childhood sex-typed behavior as a function of diagnostic status (for this analysis, the *DSM* metric was removed from the composite and served as the independent variable). With age at assessment in childhood covaried, the threshold participants had, on average, significantly more cross-sex-typed behavior in childhood ($M = .15$, $SD = .54$) than did the subthreshold participants ($M = -.31$, $SD = .36$), $F(1, 21) = 23.36$, $p < .001$, partial $\eta^2 = .53$.

Psychosexual Differentiation at Follow-Up

A summary of the psychosexual differentiation data, including gender identity at follow-up, sexual orientation, and sexual identity self-labeling for each participant, is shown in Table 3.

² These data are available in the study by Drummond (2006).

Table 3
Summary of Gender Identity and Sexual Orientation Results at Follow-Up

Participant ID	Age at assessment (years)	Age at follow-up (years)	Global Kinsey ratings		Sexual identity label	Gender identity	DSM
			Fantasy	Behavior			
1	9.74	36.58	6	6	HS	WNL	+
2	8.88	36.61	6	6	HS	WNL	+
3	5.85	32.41	0	0	HT	WNL	+
4	3.17	28.78	0	—	HT	WNL	+
5	4.92	26.61	4	0	BS	WNL	+
6 ^a	5.75	26.58	0	0	HT	WNL	+
7	12.67	17.09	—	—	AS	Dysphoric	
8	12.95	28.72	6	—	HS	WNL	
9	8.41	23.34	6	6	HT	Dysphoric	+
10	8.29	24.12	4	6	BS	WNL	+
11	4.10	20.04	0	0	HT	WNL	+
12	4.72	19.73	0	—	HT	WNL	+
13	6.70	21.53	0	0	HT	WNL	+
14	6.81	18.73	0	0	HT	WNL	+
15	12.62	23.57	6	6	HS	WNL	
16	12.16	21.10	6	6	HT	Dysphoric	+
17	7.32	17.51	0	0	HT	WNL	+
18	8.51	17.34	0	—	HT	WNL	
19 ^a	12.88	21.58	0	—	HT	WNL	
20	9.20	17.81	0	0	HT	WNL	
21	11.26	19.27	0	0	HT	WNL	+
22 ^a	12.18	17.35	—	—	HT	WNL	
23	12.45	15.44	0	—	HT	WNL	
24 ^a	11.89	27.74	0	0	HT	WNL	
25	8.79	23.12	0	0	HT	WNL	

Note. For Kinsey ratings (last 12 months), 0 = exclusively heterosexual and 6 = exclusively homosexual. In the *DSM* column, a plus sign indicates the participant met complete *DSM-III*, *DSM-III-R*, or *DSM-IV* symptom criteria for gender identity disorder at initial assessment. Dashes indicate the participant did not report fantasy or behavior. ID = identification label; HS = homosexual (lesbian); HT = heterosexual or straight; BS = bisexual; AS = asexual; WNL = within normal limits (i.e., the participant did not report any distress about being a female).

^a Participant with a disorder of sex development.

Gender Identity at Follow-up

On the basis of their answers to the semistructured clinical interview questions, participants were classified as either gender dysphoric or not gender dysphoric. In answering these questions, 22 participants (88%) reported no distress with their female gender identity at follow-up. None of the participants desired contrasex hormones or sex reassignment surgery to masculinize their bodies, nor did they express a desire to get rid of their female sex characteristics.

The remaining 3 participants (12%) were classified as gender dysphoric at follow-up (none of these 3 girls had a co-occurring DSD). Among these 3 participants, 1 had been living as a boy since early adolescence (i.e., was known to others as a boy) and was in the process of legally changing his name on official documents. The other 2 participants were living as girls, although both were often perceived of as boys by naïve others (e.g., new acquaintances, strangers, etc.), which they preferred. All 3 gender dysphoric participants wished they had been born a boy and wondered whether they would have been happier as a boy. Two of these individuals indicated a desire to have surgery to masculinize their bodies. The other participant classified as gender dysphoric reported indifference with regard to altering her physical appearance but felt that “it was better to be neutral.” On the basis of this information, 2 of the participants met *DSM-IV-TR* criteria for GID. Although the other participant did not meet full criteria for

GID, information from the clinical interview and semistructured GID interview indicated that she was gender dysphoric at follow-up.

In the Deogracias et al. (2007) study, a cutoff score of ≤ 3.00 was used to indicate “caseness” for gender dysphoria on the GIDQ-AA. The 2 participants classified as gender dysphoric (and who completed the GIDQ-AA) had scores lower than 3.00 (means of 2.19 and 2.26, respectively), whereas the 18 participants classified as not gender dysphoric (and who completed the GIDQ-AA) all had scores 3.00 ($M = 4.78$, $SD = .20$; range, 4.30–5.00). There was a significant difference between these two subgroups, $t(18) = 17.81$, $p < .001$, $d = 13.27$, which supports the classification of the participants on the basis of the clinical interview.

Bakker et al. (1993) estimated that 1 in 30,400 genetically female adults in the general population have GID. Using this baseline prevalence value, the odds of persistent gender dysphoria (12%) in the present sample was 4,084 times the odds of gender dysphoria in the general population of biological females.

Sexual Orientation

On the basis of the Kinsey interview ratings, participants were classified into the following three sexual orientation groups for fantasy and behavior: (a) heterosexual (Kinsey ratings of 0–1), (b) bisexual/homosexual (Kinsey ratings of 4–6), and (c) no sexual fantasy or behavior. For the fantasy ratings (see Table 3), 15

participants (60%) were classified as exclusively heterosexual, 8 (32%) were classified as bisexual/homosexual, and the remaining 2 (8%) were classified as having no sexual fantasies. Of the 3 participants classified as gender dysphoric, 2 were exclusively homosexual in fantasy (i.e., sexually attracted to members of their own birth sex). The other gender dysphoric participant reported no sexual fantasies and described herself as being “dead sexually.” (Of the 4 participants with a DSD, 3 were classified as exclusively heterosexual in fantasy, and 1 reported no sexual fantasies; 2 were classified as exclusively heterosexual in behavior, and 2 reported no sexual behavior.)

For the EROS, we compared the participants classified as exclusively heterosexual with those classified as bisexual/homosexual on the basis of their Kinsey ratings. With age at follow-up covaried, a 2 (sexual orientation: heterosexual vs. bisexual/homosexual) \times 2 (EROS: attraction to men vs. attraction to women) analysis of covariance (ANCOVA) revealed a significant Sexual Orientation \times EROS interaction, $F(1, 20) = 25.67, p < .001$, partial $\eta^2 = .56$.

Independent t tests showed that participants classified as heterosexual in fantasy had, on average, a higher heteroerotic EROS score ($M = 2.03, SD = .87$) than participants classified as bisexual/homosexual in fantasy ($M = 1.84, SD = 1.34$), but the difference was not significant, $t(20) < 1, d = .19$; however, participants classified as bisexual/homosexual reported, on average, a significantly higher EROS homoerotic score ($M = 3.32, SD = 1.25$) than participants classified as heterosexual ($M = 1.02, SD = .07$), $t(20) = -7.28, p < .001, d = -3.33$. A paired-samples t test was conducted to evaluate whether participants classified as heterosexual reported higher heteroerotic fantasies than homoerotic fantasies. The results indicated that the mean heteroerotic score was significantly greater than the mean homoerotic score, $t(14) = 4.75, p < .001$, with a large effect size of 1.23. Conversely, participants classified as bisexual/homosexual reported significantly higher homoerotic fantasies than heteroerotic fantasies, $t(6) = -2.61, p < .04$, with a large effect size of $-.99$.

Regarding Kinsey ratings of sexual orientation in behavior (see Table 3), 11 participants (44%) were classified as exclusively heterosexual, 6 (24%) were classified as bisexual/homosexual, and the remaining 8 (32%) were classified as having no sexual experiences. Of the 3 participants classified as gender dysphoric, 2 were exclusively homosexual in behavior (i.e., had sexual experiences with members of their own birth sex). The other gender dysphoric participant reported no sexual behaviors.

For the SHQ ratings, we compared the participants classified as exclusively heterosexual with those classified as bisexual/homosexual on the basis of their Kinsey ratings. A 2 (sexual orientation: heterosexual vs. bisexual/homosexual) \times 2 (SHQ: with men vs. with women) analysis of variance (ANOVA) revealed a significant Sexual Orientation \times SHQ interaction, $F(1, 13) = 70.41, p < .001$, partial $\eta^2 = .84$. Independent t tests for the SHQ scores showed that participants classified as heterosexual in behavior reported, on average, significantly more heterosexual sexual experiences ($M = 2.15, SD = .54$) than participants classified as bisexual/homosexual ($M = 1.00, SD = .00$), $t(13) = 4.12, p = .001, d = 2.42$. In fact, participants classified as bisexual/homosexual reported no sexual experiences with men over the past 12 months. Participants classified as bisexual/homosexual reported, on average, significantly more homosexual sexual experi-

ences ($M = 2.48, SD = .40$) than did participants classified as heterosexual ($M = 1.04, SD = .12$), $t(13) = -11.17, p < .001, d = -6.56$.

For participants classified as having a “typical” (i.e., non-gender-dysphoric) gender identity at follow-up, there were no substantive disjunctions between Kinsey ratings and sexual identity self-labeling (see Table 3). One exception was a participant who self-labeled as heterosexual, although she did not report any sexual fantasies or behaviors in the 12 months prior to the interview. For the 3 participants classified as gender dysphoric at follow-up, 2 self-labeled as heterosexual; however, it should be noted that their sexual orientation in relation to their birth sex was homosexual. As noted earlier, the remaining gender-dysphoric participant felt that she was “dead sexually” and labeled herself as asexual.

One participant (ID 5 in Table 3) was classified as bisexual/homosexual in fantasy but heterosexual in behavior. Her self-labeled sexual identity was bisexual. For the 17 participants who could be assigned a Kinsey rating between 0 and 6 for both behavior and fantasy (i.e., excluding the 8 individuals who did not report any sexual behavior [$n = 6$] or any sexual fantasy and behavior [$n = 2$]; see Table 3), the correlation between Kinsey fantasy and behavior ratings was .93 ($df = 15$), $p < .001$.

Odds Ratios for Bisexual/Homosexual Sexual Orientation in Fantasy and Behavior

Odds ratios were calculated for bisexual/homosexual sexual orientation in fantasy and behavior using prevalence estimates from several major survey studies of sexual orientation in adolescent girls and young women (Dickson, Paul, & Herbison, 2003; Fergusson, Horwood, Ridder, & Beautrais, 2005; McCabe, Hughes, Bostwick, & Boyd, 2005; Narring, Stronski, & Michaud, 2003; Remafedi, Resnick, Blum, & Harris, 1992; Russell & Seif, 2002). From these studies, base rates for bisexual/homosexual sexual orientation in fantasy and behavior were estimated to range from 2.0% to 5.0% in the female general population. The odds of reporting bisexual/homosexual sexual orientation in fantasy in the present sample was 8.9–23.1 times higher, and the odds of reporting bisexual/homosexual sexual orientation in behavior in the present sample was 6.0–15.5 times higher than it is in women in the general population.

Relation Between Age and Sexual Orientation

Table 4 shows the means and standard deviations of ages at assessment and at follow-up as a function of Kinsey groups in fantasy and behavior, respectively. For the Kinsey fantasy ratings, a one-way ANOVA for age at follow-up was significant, $F(2, 22) = 4.91, p = .017$, while the ANOVA for age at assessment in childhood approached statistical significance, $F(2, 22) = 2.58, p = .098$. At follow-up, participants classified as bisexual/homosexual were, on average, significantly older than participants classified as heterosexual or asexual, $t(21) = -2.54, p = .019$, and $t(8) = -2.37, p = .046$, respectively. There was no significant difference in the mean age at follow-up between participants classified as heterosexual and those classified as asexual, $t(15) = -1.30, p = .211$. For the Kinsey behavior ratings, the one-way ANOVAs for

Table 4
Means and Standard Deviations of Age (in Years) as a Function of Kinsey Ratings in Fantasy and Behavior

Age	None		Exclusively heterosexual		Bisexual/homosexual		<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
By Kinsey fantasy ratings ^a							
At assessment	12.42	.35	7.96	3.10	9.75	2.73	.098
At follow-up	17.22	.18	21.76	4.78	27.50	5.88	.017
By Kinsey behavior ratings ^b							
At assessment	9.94	3.99	7.51	2.51	10.02	1.91	.142
At follow-up	20.66	5.11	22.81	4.79	27.45	6.93	.087

^a For participants grouped by Kinsey fantasy ratings, $n = 2$, $n = 15$, and $n = 8$ for participants with no fantasies, exclusively heterosexual fantasies, and bisexual/homosexual fantasies, respectively. ^b For participants grouped by Kinsey behavior ratings, $n = 8$, $n = 11$, and $n = 6$ for participants with no behaviors, exclusively heterosexual behaviors, and bisexual/homosexual behaviors, respectively.

age at assessment and follow-up were nonsignificant, $F(2, 22) = 2.14$, $p = .142$, and $F(2, 22) = 2.73$, $p = .087$, respectively.

Social Desirability

One-way ANCOVAs (age at follow-up covaried) were conducted to evaluate the proportion of socially desirable responses on the M-C SDS for participants classified as heterosexual, bisexual/homosexual, and asexual in fantasy and behavior. There were no significant differences in the proportion of socially desirable responses on the M-C SDS as a function of Kinsey ratings in either fantasy or behavior, $F(2, 20) = 1.00$, ns , and $F(2, 20) < 1$, respectively (data not shown; see footnote 2).

Relation Between Sex-Typed Child Behavior and Sexual Orientation

To evaluate whether degree of cross-sex-typed behavior in childhood was related to sexual orientation at follow-up, we used the z -composite of sex-typed behavior as a function of Kinsey classification in fantasy (heterosexual, bisexual/homosexual, asexual). With age at follow-up covaried, there was no significant difference in participants' cross-sex-typed behavior in childhood as a function of sexual orientation in fantasy, $F(2, 21) = 1.06$, partial $\eta^2 = .09$ (data not shown; see footnote 2). For Kinsey ratings in behavior, however, a one-way ANCOVA was significant, $F(2, 21) = 6.45$, $p = .006$, the strength of which was large, as assessed by partial η^2 , with the Kinsey ratings accounting for 37% of the variance of participants' cross-sex-typed behavior in childhood. Participants classified as bisexual/homosexual ($M = .52$, $SD = .49$) had significantly more cross-sex-typed behavior in childhood than participants classified as heterosexual ($M = -.04$, $SD = .45$) or asexual ($M = -.33$, $SD = .39$), both $ps < .05$. There was no significant difference in the mean z -composite of sex-typed child behavior between participants classified as heterosexual and those classified as asexual (see footnote 2).

For the Kinsey ratings in behavior, we reran this analysis with the 3 gender-dysphoric participants removed (2 were classified as bisexual/homosexual and 1 was classified as asexual). For the

z -composite, the main effect for Kinsey ratings in behavior remained statistically significant, $F(2, 18) = 3.58$, $p < .05$, partial $\eta^2 = .29$.

Relation Between Recalled Childhood Cross-Gender Behavior and Gender Identity at Follow-Up

We conducted an evaluation of recalled cross-gender behavior between gender-dysphoric and non-gender-dysphoric participants. Table 5 shows the means and standard deviations of the RCGI Factor 1 score. Participants classified as gender dysphoric at follow-up ($n = 2$; $Ms = 1.29$ and 1.81 , respectively) recalled significantly more cross-gender identity and role behavior in childhood than participants classified as having no gender dysphoria

Table 5
Mean Factor Scores and Standard Deviations on the Recalled Childhood Gender Identity/Gender Role Questionnaire (Zucker et al., 2006) for Gender Identity Status and Sexual Orientation at Follow-Up

Group	M	SD	d	n
Gender identity status				
Gender dysphoric	1.55	.36	-1.96	2
No gender dysphoria	2.69	.59		18
(Adolescent girls with GID)	(2.15)	(.58)		(25)
Sexual orientation ^a				
Heterosexual	2.82	.54	1.88	15
(Heterosexual comparison sample)	(3.34)	(.53)		(30)
Bisexual/homosexual	1.84	.44		5
(Homosexual comparison sample)	(2.68)	(.72)		(21)

Note. The absolute range was 1.00–5.00. A lower score indicates more recalled atypical gender identity and gender role behavior. Twenty participants completed the questionnaire because the RCGI was not yet part of the follow-up protocol for 5 participants. Groups and values in parentheses are from Zucker et al. (2006); the factor scores were from a sample of heterosexual and homosexual female university students unselected for gender identity. GID = gender identity disorder.

^a Sexual orientation was determined on the basis of Kinsey ratings for fantasy and behavior.

($n = 18$; $M = 2.69$; range, 1.56–3.87), $t(18) = -2.62$, $p = .017$. As shown in Table 5, the mean Factor 1 score on the RCGI for the participants with persistent gender dysphoria was more extreme than it was for a sample of clinic-referred adolescent girls ($n = 25$) with GID reported on by Zucker et al. (2006), whereas the mean score of the participants without gender dysphoria was somewhat less extreme.

Further analyses on the RCGI Factor 1 score by sexual orientation revealed that participants classified as bisexual/homosexual recalled significantly more cross-gender identity and gender role behavior in childhood than did participants classified as heterosexual or asexual, $t(18) = 3.65$, $p = .002$.

Discussion

The data reported in this article represent the first systematic psychosexual follow-up into late adolescence and young adulthood of clinic-referred girls with potential problems in their gender identity development. The two key findings were as follows: (a) the percentage of girls with persistent gender dysphoria was modest but arguably higher than the base rate of GID in the general population of biological females, and (b) the percentage of girls who differentiated a later bisexual/homosexual sexual orientation was moderate but clearly higher than the base rates of bisexual/homosexual sexual orientation in general survey and epidemiological studies of adolescent girls and young adult women in which sexual orientation (in fantasy and/or behavior) was assessed with at least some gradation in response options (as opposed to simple dichotomous items).

Before providing an analysis of these findings, we note two limitations of the study. First, the sample size was small, but this is, at least in part, understandable because the number of referred girls to specialized gender identity clinics is notably lower than that of referred boys (e.g., Cohen-Kettenis et al., 2003, 2006). Second, the present study did not have a concurrent control group (e.g., a group of girls referred for other kinds of clinical concerns or a group of nonreferred girls). Accordingly, some of our comparative analyses relied on epidemiological or survey data.

Regarding the persistence of gender dysphoria from the childhood assessment to the follow-up, the present study found that the vast majority of the girls showed desistance: 88% of the girls did not report distress about their gender identity at follow-up. The high rate of desistance appears to differ quite markedly from the findings of other follow-up studies of adolescent girls and adult women with GID (in which the baseline assessment is in adolescence or adulthood). In these studies, the rate of GID persistence appears to be, at minimum, around 70% (Cohen-Kettenis & van Goozen, 1997; Smith, van Goozen, Kuiper, & Cohen-Kettenis, 2005). In a comparative developmental perspective, then, there appears to be important variation in GID persistence between childhood and adolescence/young adulthood.

How might this disjunction be understood? One possibility pertains to the differences in the *DSM* criteria for GID that are used for children versus those that are used for adolescents/adults. The criteria for GID in girlhood place relatively greater weight on surface behaviors of cross-gender identification, whereas the criteria in adolescence and adulthood rely more strongly on behaviors and feelings pertaining to the disjunction between gender subjectivity and somatic sex. Thus, it is conceivable that the childhood

criteria for GID may “scoop in” girls who are at relatively low risk for adolescent/adult gender dysphoria, which revolves so much around somatic indicators (e.g., distress regarding breast development or other markers of physical femaleness, etc.).

It should, however, be noted that adolescent girls and adult women with GID typically recall the same kinds of cross-gender behavior patterns in girlhood that correspond to the *DSM* criteria for GID in childhood (e.g., Blanchard & Freund, 1983; Pearlman, 2006; Zucker et al., 2006), which are then augmented and exacerbated by the external physical markers of biological femaleness at puberty. Indeed, in the present study, the recalled sex-typed behavior from childhood of our participants was reasonably similar to the childhood recollections of girls with GID assessed for the first time in adolescence (see Table 5).

In the present study, 40% of the girls were not judged to have met the complete *DSM* criteria for GID at the time of childhood assessment (although some of these girls likely had met the complete criteria at some earlier point in their development). Thus, on the one hand, it could be argued that if some of the girls were subthreshold for GID in childhood, then one might assume that they would not be at risk for GID in adolescence or adulthood. On the other hand, it could be argued that cross-gender identification in girlhood (including subthreshold GID) is a risk factor for later GID; that is, under some conditions, there is an intensification of cross-gender identification that results in the development of gender dysphoria (see Green, 2003). Indeed, clinical experience with adolescent girls with GID indicates that not all of them would have met the complete criteria for GID in girlhood. Indeed, it is not uncommon for the parents of these girls to recall that their daughters identified as “tomboys” during childhood and that they did not remember them voicing the desire to want to become a boy, but that their gender dysphoria emerged only around the time of puberty (see, e.g., Pearlman, 2006; Zucker, 2006, Case 1).

If one accepts the argument that girlhood cross-gender identification is a risk factor for gender dysphoria in adolescence and adulthood, the relatively high rate of desistance in the current study (in comparison with the relatively high rate of persistence seen in gender-dysphoric girls and women assessed for the first time in adolescence or adulthood) suggests that there is some type of plasticity in gender identity differentiation that operates early in development but then narrows considerably by adolescence. Thus, at least among the girls in the present sample, some factor or set of factors may have operated to lessen the likelihood that their gender dysphoria or cross-gender identification would persist or intensify in adolescence and adulthood. Of course, such factors could include both biological and psychosocial influences, but the systematic identification of such factors was beyond the scope of the present investigation.

To our knowledge, the results of the present study represent the first prospective data set that shows that girlhood cross-gender identification is associated with a relatively high rate of bisexual/homosexual sexual orientation in adolescence and adulthood. Using survey data on sexual orientation in young women as a comparative metric, we estimated that the odds of reporting a bisexual/homosexual sexual orientation in fantasy was 8.9–23.1 times higher in the present sample and that the odds of reporting a bisexual/homosexual sexual orientation in behavior was 6.7–15.5 times higher. In this respect, the data show at least some conver-

gence with data from retrospective studies (Bailey & Zucker, 1995).

A strength of the present study was that the assessment of sexual orientation was based on a multiparameter, face-to-face interview from which Kinsey global ratings were derived and that was complemented by self-report on psychometrically sound questionnaires (cf. Savin-Williams, 2006). Although one has to be cautious about the possibility that our participants underreported a minority sexual orientation, it should be recalled that we found no significant relation between our Kinsey classifications and the propensity to give socially desirable responses on the M-C SDS.

Our classification of participants' sexual orientation was based on fantasy and behavior ratings for the 12-month period prior to follow-up. In the literature on women's sexual orientation, there has been a lot of recent discussion regarding its stability versus its fluidity (see, e.g., Baumeister, 2000; Peplau et al., 1999). Diamond (2005b), for example, followed 79 self-labeled lesbian, bisexual, and "unlabeled" sexual minority women over an 8-year period (mean age at baseline, 19 years). At the 8-year follow-up, 92.4% of the women continued to self-label as lesbian, bisexual, or unlabeled, although there was considerable fluctuation within these three categories over time (e.g., lesbian to bisexual or unlabeled to lesbian). The remaining 7.5% of the women self-labeled as heterosexual at the follow-up. In our view, Diamond's (2005b) data suggest considerable stability of a minority sexual orientation despite the evidence of greater fluidity within the subcategories of lesbian, bisexual, and unlabeled.

One limitation of Diamond's study was that it did not include a group of self-labeled heterosexual women at baseline; thus, comparative evidence on the stability or fluidity of a majority sexual orientation was not available. Using data from the National Longitudinal Survey of Adolescent Health, however, Savin-Williams and Ream (2007) provided data on the stability of a heterosexual sexual orientation (attraction and behavior) of several thousand girls and women between the ages of 15 and 26 years in a three-wave assessment. In their study, there was considerable evidence for a stable heterosexual sexual orientation. For example, only 3.1% of girls who reported exclusive heterosexual attractions at Wave 1 reported bisexual or lesbian attractions at Wave 3, and only 3.5% of girls who reported exclusive heterosexual behavior at Wave 1 reported bisexual or lesbian behavior at the Wave 3. Given these findings, the case could be made that our participants' sexual orientations will remain relatively stable over time but, on this point, only continued follow-up can test this conjecture empirically.

Because there was considerable variability in sexual orientation at follow-up, we made some relatively crude efforts at predicting such variation (compromised, of course, by the small sample size). There were hints in the data that younger age at assessment in childhood was associated with a later heterosexual sexual orientation (Table 4), but the effects were weak. The composite index of sex-typed behavior in childhood was not significantly associated with sexual orientation in fantasy, but it was with sexual orientation in behavior, with those participants classified as bisexual/homosexual exhibiting more cross-gender behavior. We also found that participants classified as bisexual/homosexual recalled having engaged in more cross-gender behavior during childhood than those classified as heterosexual or asexual (Table 5). These data are suggestive, therefore, of a "dosage" effect, that is, that

degree of girlhood cross-gender identification is associated with a greater likelihood of a later minority sexual orientation. Of course, these preliminary findings need to be confirmed in much larger clinical samples; in addition, it would be desirable to examine whether or not variation in degree of girlhood cross-sex-typed behavior is related to sexual orientation in epidemiological samples drawn from nonclinical populations.

How do the results of the present study compare with those of follow-up studies of boys with GID? In Zucker (2005b), a follow-up on 40 boys with GID from the same clinic, using the same methods as in the present study, showed a persistence rate of 20%, only modestly higher than the rate of 12% for the girls in the present study. In Zucker (2005b), 42.5% of the boys were classified as bisexual/homosexual in fantasy, which is again only modestly higher than the rate of 32% for the girls in the present study; however, the rate of a bisexual/homosexual sexual orientation in fantasy was considerably lower than the 75% found by Green (1987) in his study of feminine boys. In comparison with the boys followed up by Green (1987) and by Zucker (2005b), it is important to note that the girls in the present study were, on average, several years older at follow-up, which, if anything, would suggest that the likelihood of underreporting a minority sexual orientation would be lower for this sample than for the samples of boys.

If it proves to be the case that cross-sex-typed behavior is, indeed, less closely linked to a later bisexual/homosexual sexual orientation in girls than it is in boys, this would be consistent with a prediction made by Bailey and Zucker (1995) in their meta-analytic retrospective study. It would also be consistent with recent theorizing on the greater flexibility of sexual orientation in women, in which it has been argued that relational factors during adolescence and adulthood play a more important role in sexual partner preference than it does in men (Diamond, 2003, 2005a; Peplau et al., 1999). It is apparent from the present study that there is considerable within-sex variation to be explained in the long-term psychosexual differentiation of behaviorally masculine girls, with regard to both gender identity and sexual orientation. These findings suggest that any reductionist account of psychosexual differentiation will likely be unable to capture this variation. Multivariate models are clearly required in order to identify the best predictors of such within-sex variation. On this point, the field will hopefully move forward as larger samples are collated, including prospective, epidemiologically based cohorts that incorporate theoretically based predictor variables.

References

- American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: Author.
- American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.
- American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- Bailey, J. M., Bechtold, K. T., & Berenbaum, S. A. (2002). Who are tomboys and why should we study them? *Archives of Sexual Behavior*, 31, 333–341.
- Bailey, J. M., & Zucker, K. J. (1995). Childhood sex-typed behavior and sexual orientation: A conceptual analysis and quantitative review. *Developmental Psychology*, 31, 43–55.

- Bakker, A., van Kesteren, P. J. M., Gooren, L. J. G., & Bezemer, P. D. (1993). The prevalence of transsexualism in the Netherlands. *Acta Psychiatrica Scandinavica*, 87, 237–238.
- Barrett, A. E., & White, H. R. (2002). Trajectories of gender role orientation in adolescence and early adulthood: A prospective study of the mental health effects of masculinity and femininity. *Journal of Health and Social Behavior*, 43, 451–468.
- Bartlett, N. H., & Vasey, P. L. (2006). A retrospective study of childhood gender-atypical behavior in Samoan *Fa'afafine*. *Archives of Sexual Behavior*, 35, 659–666.
- Bates, J. E., & Bentler, P. M. (1973). Play activities of normal and effeminate boys. *Developmental Psychology*, 9, 20–27.
- Baumeister, R. F. (2000). Gender differences in erotic plasticity: The female sex drive as socially flexible and responsive. *Psychological Bulletin*, 126, 347–374.
- Berenbaum, S. A., & Bailey, J. M. (2003). Effects on gender identity of prenatal androgens and genital appearance: Evidence from girls with congenital adrenal hyperplasia. *Journal of Clinical Endocrinology & Metabolism: Clinical and Experimental*, 88, 1101–1106.
- Blanchard, R., & Freund, K. (1983). Measuring masculine gender identity in females. *Journal of Consulting and Clinical Psychology*, 51, 205–214.
- Cohen-Kettenis, P. T., Owen, A., Kaijser, V. G., Bradley, S. J., & Zucker, K. J. (2003). Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: A cross-national, cross-clinic comparative analysis. *Journal of Abnormal Child Psychology*, 31, 41–53.
- Cohen-Kettenis, P. T., & Pfäfflin, F. (2003). *Transgenderism and intersexuality in childhood and adolescence: Making choices*. Thousand Oaks, CA: Sage.
- Cohen-Kettenis, P. T., & van Goozen, S. H. M. (1997). Sex reassignment of adolescent transsexuals: A follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36, 263–271.
- Cohen-Kettenis, P. T., Wallien, M., Johnson, L. L., Owen-Anderson, A. F. H., Bradley, S. J., & Zucker, K. J. (2006). A parent-report Gender Identity Questionnaire for Children: A cross-national, cross-clinic comparative analysis. *Clinical Child Psychology and Psychiatry*, 11, 397–405.
- Cohler, B. J., & Galatzer-Levy, R. M. (2000). *The course of gay and lesbian lives: Social and psychoanalytic perspectives*. Chicago: University of Chicago Press.
- Crowne, D. P., & Marlowe, D. (1960). A new scale of social desirability independent of psychopathology. *Journal of Consulting Psychology*, 24, 349–354.
- Deogracias, J. J., Johnson, L. L., Meyer-Bahlburg, H. F. L., Kessler, S. J., Schober, J. M., & Zucker, K. J. (2007). The Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults. *Journal of Sex Research*, 44, 370–379.
- Diamond, L. M. (2003). What does sexual orientation orient? A biobehavioral model distinguishing romantic love and sexual desire. *Psychological Review*, 110, 173–192.
- Diamond, L. M. (2005a). From the heart or the gut? Sexual-minority women's experiences of desire for same-sex and other-sex partners. *Feminism & Psychology*, 15, 10–14.
- Diamond, L. M. (2005b). A new view of lesbian subtypes: Stable versus fluid identity trajectories over an 8-year period. *Psychology of Women Quarterly*, 29, 119–128.
- Dickson, N., Paul, C., & Herbison, P. (2003). Same-sex attraction in a birth cohort: Prevalence and persistence in early adulthood. *Social Science & Medicine*, 56, 1607–1615.
- Doorn, C. D., Poortinga, J., & Verschoor, A. M. (1994). Cross-gender identity in transvestites and male transsexuals. *Archives of Sexual Behavior*, 23, 185–201.
- Drummond, K. D. (2006). *A follow-up study of girls with gender identity disorder*. Unpublished master's thesis, Ontario Institute for Studies in Education of the University of Toronto, Toronto, Ontario, Canada.
- Ehrhardt, A. A., Grisanti, G., & McCauley, E. A. (1979). Female-to-male transsexuals compared to lesbians: Behavioral patterns of childhood and adolescent development. *Archives of Sexual Behavior*, 8, 481–490.
- Fergusson, D. M., Horwood, L. J., Ridder, E. M., & Beautrais, A. L. (2005). Sexual orientation and mental health in a birth cohort of young adults. *Psychological Medicine*, 35, 971–981.
- Freund, K., Langevin, R., Satterberg, J., & Steiner, B. (1977). Extension of the Gender Identity Scale for Males. *Archives of Sexual Behavior*, 6, 507–519.
- Fridell, S. R., Owen-Anderson, A., Johnson, L. L., Bradley, S. J., & Zucker, K. J. (2006). The Playmate and Play Style Preferences Structured Interview: A comparison of children with gender identity disorder and controls. *Archives of Sexual Behavior*, 35, 729–737.
- Gottschalk, L. (2003). Same-sex sexuality and childhood gender non-conformity: A spurious connection. *Journal of Gender Studies*, 12, 35–50.
- Green, R. (1987). *The "sissy boy syndrome" and the development of homosexuality*. New Haven, CT: Yale University Press.
- Green, R. (2003). The "T" word [Letter to the editor]. *Archives of Sexual Behavior*, 32, 1.
- Green, R., Williams, K., & Goodman, M. (1982). Ninety-nine "tomboys" and "non-tomboys": Behavioral contrasts and demographic similarities. *Archives of Sexual Behavior*, 11, 247–266.
- Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: Review of the evidence. *Journal of Child Psychology and Psychiatry*, 45, 260–273.
- Hegarty, P. (1999). *Recalling childhood, constructing identity: Norms and stereotypes in theories of sexual orientation*. Unpublished doctoral dissertation, Stanford University, Stanford, CA.
- Holden, R. R., & Fekken, G. C. (1989). Three common social desirability scales: Friends, acquaintances, or strangers? *Journal of Research in Personality*, 23, 180–191.
- Hollingshead, A. B. (1975). *Four factor index of social status*. Unpublished manuscript, Department of Sociology, Yale University, New Haven, CT.
- Hughes, I. A., Houk, C., Ahmed, S. F., Lee, P. A., & Lawson Wilkins Pediatric Endocrine Society/European Society for Paediatric Endocrinology Consensus Group. (2006). Consensus statement on management of intersex disorders. *Archives of Disease in Childhood*, 91, 554–563.
- Hyde, J. S. (2005). The gender similarities hypothesis. *American Psychologist*, 60, 581–592.
- Johnson, L. L., Bradley, S. J., Birkenfeld-Adams, A. S., Radzins Kuksis, M. A., Maing, D. M., Mitchell, J. N., & Zucker, K. J. (2004). A parent-report Gender Identity Questionnaire for Children. *Archives of Sexual Behavior*, 33, 105–116.
- Khuri, J., & Ruble, D. N. (2006, April). *The consequences of early gender-typicality: Findings in a female sample*. Poster session presented at the Second Gender Development Conference, San Francisco, CA.
- King, M. F., & Brunner, G. C. (2000). Social desirability bias: A neglected aspect of validity testing. *Psychology and Marketing*, 17, 79–103.
- Kinsey, A. C., Pomeroy, W. B., & Martin, C. E. (1948). *Sexual behavior in the human male*. Philadelphia: W. B. Saunders.
- Kite, M. E., & Deaux, K. (1987). Gender belief systems: Homosexuality and the implicit inversion theory. *Psychology of Women Quarterly*, 11, 83–96.
- Langevin, R. (1985). *Sexual strands: Understanding and treating sexual anomalies in men*. Hillsdale, NJ: Erlbaum.
- Laumann, E. O., Gagnon, J. H., Michael, R. T., & Michaels, S. (1994). *The social organization of sexuality: Sexual practices in the United States*. Chicago: University of Chicago Press.
- Lippa, R. (1998). Gender-related individual differences and the structure of vocational interests: The importance of the people-things dimension. *Journal of Personality and Social Psychology*, 74, 996–1009.

- Lippa, R. A. (2002). *Gender, nature, and nurture*. Mahwah, NJ: Erlbaum.
- Liss, M. B. (Ed.). (1983). *Social and cognitive skills: Sex roles and children's play*. New York: Academic Press.
- Maccoby, E. E. (1998). *The two sexes: Growing up apart, coming together*. Cambridge, MA: Belknap Press.
- McCabe, S. E., Hughes, T. L., Bostwick, W., & Boyd, C. J. (2005). Assessment of difference in dimensions of sexual orientation: Implications for substance use research in a college-age population. *Journal of Studies on Alcohol*, 66, 620–629.
- Meyer-Bahlburg, H. F. L. (1994). Intersexuality and the diagnosis of gender identity disorder. *Archives of Sexual Behavior*, 23, 21–40.
- Meyer-Bahlburg, H. F. L. (2005). Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. *Archives of Sexual Behavior*, 34, 423–438.
- Narring, F., Stronski, H. S., & Michaud, P.-A. (2003). Prevalence and dimensions of sexual orientation in Swiss adolescents: A cross-sectional survey of 16- to 20-year-old students. *Acta Paediatrica*, 92, 233–239.
- Pearlman, S. F. (2006). Terms of connection: Mother-talk about female-to-male transgender children. *Journal of GLBT Family Studies*, 2(3/4), 93–122.
- Peplau, L. A., & Huppert, M. (in press). Masculinity, femininity and the development of sexual orientation. *Journal of Gay and Lesbian Psychotherapy*.
- Peplau, L. A., Spalding, L. R., Conley, T. D., & Veniegas, R. C. (1999). The development of sexual orientation in women. *Annual Review of Sex Research*, 10, 70–99.
- Remafedi, G., Resnick, M., Blum, R., & Harris, L. (1992). Demography of sexual orientation in adolescents. *Pediatrics*, 89, 714–721.
- Ruble, D. N., Martin, C. L., & Berenbaum, S. A. (2006). Gender development. In W. Damon & R. M. Lerner (Series Eds.) and N. Eisenberg (Vol. Ed.), *Handbook of child psychology* (6th ed.), Vol. 3: *Social, emotional, and personality development* (pp. 858–932). New York: Wiley.
- Russell, S. T., & Seif, H. (2002). Bisexual female adolescents: A critical analysis of past research, and results from a national survey. *Journal of Bisexuality*, 2(2–3), 73–94.
- Savin-Williams, R. C. (2006). Who's gay? Does it matter? *Current Directions in Psychological Science*, 15, 40–44.
- Savin-Williams, R. C., & Ream, G. L. (2007). Prevalence and stability of sexual orientation components during adolescence and young adulthood. *Archives of Sexual Behavior*, 36, 385–393.
- Silverthorn, N. A., & Gekoski, W. L. (1995). Social desirability effects on measures of adjustment to university, independence from parents, and self-efficacy. *Journal of Clinical Psychology*, 51, 244–251.
- Smith, Y. L. S., van Goozen, S. H. M., Kuiper, A. J., & Cohen-Kettenis, P. T. (2005). Sex reassignment: Outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychological Medicine*, 35, 89–99.
- Storrs, M. D. (1980). Theories of sexual orientation. *Journal of Personality and Social Psychology*, 38, 783–792.
- Strahan, R., & Gerbasi, K. C. (1972). Short, homogeneous versions of the Marlowe-Crowne Social Desirability Scale. *Journal of Clinical Psychology*, 28, 191–193.
- Thorndike, R. L., Hagen, E. P., & Sattler, J. M. (1986). *Stanford-Binet Intelligence Scale* (4th ed.). Chicago: Riverside.
- Wechsler, D. (1974). *Manual: Wechsler Intelligence Scale for Children—Revised*. New York: Psychological Corporation.
- Wechsler, D. (1991). *Wechsler Intelligence Scale for Children—Third Edition*. San Antonio, TX: Psychological Corporation.
- Wechsler, D. (1997). *Wechsler Adult Intelligence Scale—Third Edition*. San Antonio, TX: Psychological Corporation.
- Wechsler, D. (2002). *Wechsler Preschool and Primary Scale of Intelligence—Third Edition*. San Antonio, TX: Psychological Corporation.
- Zucker, K. J. (2005a). Commentary on Gottschalk's (2003) "Same-sex sexuality and childhood gender non-conformity: A spurious connection." *Journal of Gender Studies*, 14, 55–60.
- Zucker, K. J. (2005b). Gender identity disorder in children and adolescents. *Annual Review of Clinical Psychology*, 1, 467–492.
- Zucker, K. J. (2005c). Measurement of psychosexual differentiation. *Archives of Sexual Behavior*, 34, 375–388.
- Zucker, K. J. (2006). Gender identity disorder. In D. A. Wolfe & E. J. Mash (Eds.), *Behavioral and emotional disorders in adolescents: Nature, assessment, and treatment* (pp. 535–562). New York: Guilford Press.
- Zucker, K. J. (in press). Reflections on the relation between sex-typed behavior in childhood and sexual orientation in adulthood. *Journal of Gay & Lesbian Psychotherapy*.
- Zucker, K. J., & Bradley, S. J. (1995). *Gender identity disorder and psychosexual problems in children and adolescents*. New York: Guilford Press.
- Zucker, K. J., Bradley, S. J., Lowry Sullivan, C. B., Kuksis, M., Birkenfeld-Adams, A., & Mitchell, J. N. (1993). A gender identity interview for children. *Journal of Personality Assessment*, 61, 443–456.
- Zucker, K. J., Bradley, S. J., Oliver, G., Blake, J., Fleming, S., & Hood, J. (1996). Psychosexual development of women with congenital adrenal hyperplasia. *Hormones and Behavior*, 30, 300–318.
- Zucker, K. J., Doering, R. W., Bradley, S. J., & Finegan, J. K. (1982). Sex-typed play in gender-disturbed children: A comparison to sibling and psychiatric controls. *Archives of Sexual Behavior*, 11, 309–321.
- Zucker, K. J., Finegan, J. K., Doering, R. W., & Bradley, S. J. (1983). Human figure drawings of gender-problem children: A comparison to siblings, psychiatric, and normal controls. *Journal of Abnormal Child Psychology*, 11, 287–298.
- Zucker, K. J., Lozinski, J. A., Bradley, S. J., & Doering, R. W. (1992). Sex-typed responses in the Rorschach protocols of children with gender identity disorder. *Journal of Personality Assessment*, 58, 295–310.
- Zucker, K. J., Mitchell, J. N., Bradley, S. J., Tkachuk, J., Cantor, J. M., & Allin, S. M. (2006). The Recalled Childhood Gender Identity/Gender Role questionnaire: Psychometric properties. *Sex Roles*, 54, 469–483.

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EXHIBIT F

Psychosexual Outcome of Gender-Dysphoric Children

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ABSTRACT

Objective: To establish the psychosexual outcome of gender-dysphoric children at 16 years or older and to examine childhood characteristics related to psychosexual outcome. **Method:** We studied 77 children who had been referred in childhood to our clinic because of gender dysphoria (59 boys, 18 girls; mean age 8.4 years, age range 5–12 years). In childhood, we measured the children's cross-gender identification and discomfort with their own sex and gender roles. At follow-up 10.4 ± 3.4 years later, 54 children (mean age 18.9 years, age range 16–28 years) agreed to participate. In this group, we assessed gender dysphoria and sexual orientation. **Results:** At follow-up, 30% of the 77 participants (19 boys and 4 girls) did not respond to our recruiting letter or were not traceable; 27% (12 boys and 9 girls) were still gender dysphoric (persistence group), and 43% (desistance group: 28 boys and 5 girls) were no longer gender dysphoric. Both boys and girls in the persistence group were more extremely cross-gendered in behavior and feelings and were more likely to fulfill gender identity disorder (GID) criteria in childhood than the children in the other two groups. At follow-up, nearly all male and female participants in the persistence group reported having a homosexual or bisexual sexual orientation. In the desistance group, all of the girls and half of the boys reported having a heterosexual orientation. The other half of the boys in the desistance group had a homosexual or bisexual sexual orientation. **Conclusions:** Most children with gender dysphoria will not remain gender dysphoric after puberty. Children with persistent GID are characterized by more extreme gender dysphoria in childhood than children with desisting gender dysphoria. With regard to sexual orientation, the most likely outcome of childhood GID is homosexuality or bisexuality. *J. Am. Acad. Child and Adolesc. Psychiatry*, 2008;47(12):1413–1423. **Key Words:** gender identity disorder, gender dysphoria, pubertal outcome, psychosexual differentiation, sexual orientation.

Children diagnosed with gender identity disorder (GID) have a strong cross-gender identification and a persistent discomfort with their biological sex or gender role associated with that sex (gender dysphoria). Initial studies have shown that most children with GID will no longer be gender dysphoric later in life.^{1–7} However, a

few more recent articles^{8,9} indicated that the psychosexual differentiation of children with GID is more variable than what the early studies suggested and that, in a substantial proportion of the children (20%), the gender-dysphoric feelings persist into adolescence.

With *DSM-V* on the horizon, an important diagnostic issue concerns the relation between childhood and adolescent/adult GID. Some critics have expressed concerns that the *DSM*^{10,11} criteria do not adequately differentiate the children with “true” (and probably persistent) GID from those who show merely gender-nonconforming behavior¹² and that, as a consequence, children who should not be classified as having a psychiatric disorder would be treated with various psychological interventions. Clinically, it is also important to be able to discriminate between persisters and desisters before the start of puberty. If one was certain that a child belongs to the persisting group, interventions with gonadotropin-releasing hormone (GnRH) analogs to delay puberty could even start before puberty

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This article is the subject of an editorial by Dr. Kenneth Zucker in this issue.

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rather than after the first pubertal stages, as now often happens.¹³ The possibility of identifying the persisters in childhood would also be helpful, if treatments would be available to prevent the intensive and drastic hormonal and surgical treatments these children face in adolescence or adulthood.

Another issue regarding the psychosexual outcome of children with GID is the relation between the child's gender atypicality and sexual orientation in adulthood. Early prospective follow-up studies indicated that a high rate (60%–100%) of children (mostly boys) with gender dysphoria had a homosexual or bisexual sexual orientation in adolescence or adulthood and no longer experienced gender-dysphoric feelings.^{1–8} In a prospective follow-up study by Green,³ sexual orientation and gender identity in adulthood were assessed in 44 feminine boys and 30 control boys. Of these 44 feminine boys, only one youth was gender dysphoric at the age of 18, whereas none of the control boys reported gender dysphoria at follow-up. Sexual orientation in fantasy and behavior was assessed by means of a semi-structured interview. Green found that, on the behavior dimension, 80% of the feminine boys were either homosexual or bisexual, and, on the fantasy dimension, 75% of the feminine boys had a homosexual or a bisexual sexual orientation at follow-up. Among the control boys, the ratings were 4% for behavior and 0% for fantasy. Green and colleagues¹⁴ also found that sexual orientation was associated with childhood doll play and female role playing. The results of Green and others^{1–7} are in accordance with retrospective studies among adult homosexuals, who recalled more childhood cross-gender behavior than heterosexuals.¹⁵

The earlier follow-up studies^{1–9} indicated that the percentages of gender-dysphoric boys and girls who had a later bisexual/homosexual orientation were much higher than the base rates of bisexuality or homosexuality in general surveys and in epidemiological studies of adolescents and young adults. The reported percentages are lower in the study by Zucker and Bradley⁸ on (mostly) gender-dysphoric boys (31% of the 41 participants who had sexual fantasies had either a bisexual or homosexual sexual orientation in fantasy; for 58%, no data on sexual behavior were available) and in a study by Drummond et al.¹⁶ among 25 gender-dysphoric girls (32% of the girls reported having bisexual or homosexual fantasies; there were no data on sexual behavior for 32% of the girls), but in both studies, the proportion of

participants with a homosexual and bisexual sexual orientation was still substantially higher than the base rates in the general population.

Because a gender-dysphoric outcome was not common in the above studies, the studies^{1–9} focused more on the sexual orientation outcome of the gender-dysphoric children than on the relation between childhood gender dysphoria and later GID. Therefore, these reports do not give information on whether participants with distinct gender identity outcomes differ from each other in childhood. It has been argued that there is plasticity in gender identity differentiation that occurs in early development and narrows considerably by adolescence,¹⁶ but the precise factor or set of factors influencing psychosexual development is still unknown. It is likely that only the children with extreme gender dysphoria are future sex reassignment applicants, whereas the children with less persistent and intense gender dysphoria are future homosexuals or heterosexuals without GID. However, none of the follow-up studies have as yet provided evidence for this supposition.

In this study, we first assessed the psychosexual outcome of gender-dysphoric boys and girls in terms of gender identity and sexual orientation. Second, we investigated which childhood measures of gender behavior and feelings were related to GID persistence or desistance. Based on our clinical experience, we expected the more extreme gender-dysphoric children to be persisters.

METHOD

Participants

Between 1989 and 2005, 200 children (144 boys and 56 girls) were referred to the Gender Identity Clinic of the Department of Child and Adolescent Psychiatry at the University Medical Center Utrecht (which moved to the Department of Medical Psychology of the VU University Medical Center in Amsterdam in 2002). To be included in the follow-up study, participants had to be at least 16 years of age. Using this cutoff, we identified 77 children (59 boys and 18 girls, who were between 5 and 12 years of age at first assessment). All 77 children were contacted for participation.

Table 1 provides participant characteristics at childhood assessment (T_0) and follow-up assessment (T_1). At T_0 , 75% of the 77 potential participants who were contacted had met complete diagnostic criteria for GID, according to the *DSM-III-R*,²⁰ whereas 25% were subthreshold for the diagnosis (GID not otherwise specified [NOS]).²⁰

At T_1 , 23 of the 77 potential participants (30%; 19 boys and 4 girls) did not respond or were not traceable (nonresponder group); the other 54 (40 boys and 14 girls) were included in our study.

TABLE 1
Demographic Characteristics, IQ, and DSM Diagnosis of GID at T₀ and T₁

Variables	All (N = 77)			Persistence (n = 21)		Desistance (n = 23)		Parent (n = 10)		Nonresponders (n = 4)	
	Boys (n = 59)	Girls (n = 18)		Boys (n = 12)	Girls (n = 9)	Boys (n = 19)	Girls (n = 4)	Boys (n = 9)	Girls (n = 1)	Boys (n = 19)	Girls (n = 4)
Age at childhood assessment											
Mean	8.3	8.6		8.6	8.8	8.7	8.3	8.1	9	7.9	8.5
SD	2.0	1.5		1.4	1.8	2.4	1.9	2.3	0	1.8	1.8
Range	5–12	6–11		6–11	6–11	5–12	7–11	5–12	0	5–11	7–9
Age at follow-up assessment											
Mean	19.4	18.7		19.1	17.8	19.8	18.3	17.8	25	19.8	19.8
SD	3.4	2.7		2.9	2.5	3.3	1.3	1.4	0	4.3	2.2
Range	16–28	16–25		16–24	16–24	16–28	17–2	16–20	0	16–24	17–22
Interval, y ^a											
Mean	10.4	10.1		10.5	9.0	9.9	10.0	8.8	16	11.6	11.3
SD	3.4	3.8		3.7	4.3	3.2	4.3	3.1	0	3.4	2.8
Marital status ^b											
Two parents, n	42	11		9	8	15	2	7	0	11	1
Other family/institution, n	12	5		3	1	4	2	0	0	5	2
Total IQ ^c											
Mean	96.7	103.2		92.2	101	101.8	107.3	99.3	122	92.5	91.7
SD	16.1	23.4		14.2	20.2	13.4	31.4	20.3	0	17.1	28.0
Range	67–131	61–129		67–114	74–128	79–129	61–129	70–131	0	68–129	74–124
Nationality											
Dutch, n	50	16		10	8	15	4	9	1	16	3
Other, n	9	2		2	1	4	0	0	0	3	1
Childhood GID diagnosis, n	44	14		12	9	12	3	5	1	15	1
Childhood GID NOS diagnosis, n	15	4		0	0	7	1	4	0	4	3

Note: GID = gender identity disorder; NOS = not otherwise specified.

^aInterval denotes the time between childhood assessment and follow-up assessment.

^bFor marital status, we asked whether the children were living with two parents or had another family composition. For seven children, there were no data on marital status.

^cIQ was assessed with Dutch versions of the Wechsler Preschool and Primary Scale of Intelligence¹⁷ or the WISC.^{18,19} For five boys and two girls, there were no IQ data.

Twenty-one participants (27%; 9 girls and 12 boys) were still gender dysphoric at follow-up (persistence group). All of these persisters had met the complete diagnostic criteria for GID according to the *DSM-IV*¹⁰ or the *DSM-IV-TR*¹¹ at follow-up and had applied for sex reassignment at the Gender Identity Clinic before the age of 16. They had subsequently followed a standardized diagnostic protocol. This implies that information is obtained from the adolescents and their parents or caretakers on various aspects of their general and psychosexual development since the last contact with the clinic and on their current functioning. The procedure also includes a psychodiagnostic assessment, a child psychiatric evaluation (by a different clinician than the diagnostician), and often a family evaluation (for more information on the clinical procedure, see Reference 21). In this group, we found a significant sex difference ($\chi^2_1 = 5.129, p < .05$): 50% of the girls and 20% of the boys had persisting gender dysphoria (Table 1). Because of this significant sex difference, we analyzed our data separately by sex.

Twenty-three participants (30%; 19 boys, 4 girls) were visited at home because they had no longer been seen at the clinic after childhood (desistance group). Ten participants (13%) did not want to participate themselves, but they allowed their parents to fill out a questionnaire. This parent group consisted of 9 boys and 1 girl. Because there were no significant differences between the desistance group and the parent group for all background variables (marital status: $\chi^2_3 = 4.41, p > .05$; diagnoses in childhood ($\chi^2_1 = 0.676, p > .05$); nationality: ($\chi^2_4 = 2.56, p > .05$); full-scale IQ ($z = -0.27, p = .80$); and psychological functioning, as measured by the Child Behavior Checklist (CBCL; total T scores [$z = -0.88, p > .05$], internalizing T scores [$z = -0.84, p > .05$], or externalizing T scores [$z = -1.17, p > .05$]), the participants in the parent group were included in the desistance group. Therefore, the desistance group consisted of 33 participants (28 boys and 5 girls).

Table 1 shows the background data and age for the children at T_0 and for the four different groups at T_1 . There were no data on marital status for 7 participants because three parents of adolescents (parent group) did not provide this information, and for four children from the nonresponder group, we had no childhood data on marital status. Furthermore, we had no total IQ scores for 5 boys and 2 girls because their intelligence had not been assessed in childhood. Three of these boys belonged to the nonresponder group, one boy to the persistence group, and one boy belonged to the desistance group. One of the two girls belonged to the persistence group, and the other to the desistance group. No significant age differences were found between the groups.

Because there were no differences between the nonresponder and the desistance group, or between the nonresponder and the parent group on all scales of the CBCL and on background variables, the desistance group seems to be representative of all subjects who did not seek sex reassignment after puberty.

Measures

Background Measures and DSM Diagnosis. Diagnoses and five background measures were obtained from the medical charts at childhood assessment: age at assessment, sex, parents' marital status, total IQ, and nationality. Information provided by the parents (clinical interviews on gender development and current gender role behavior, Gender Identity Questionnaire for Children [GIQC; for a description of the GIQC, see below]), the child (clinical interviews on current and past peer and play preferences, gender role behavior and identity status, Gender Identity Interview for Children [GIIC; for a description, see below], a standardized play observation, and the

Draw-a-Person test), and teachers (by means of a self-developed teacher questionnaire and the Teacher's Report Form, a teacher version of the CBCL²²), during a standardized clinical assessment procedure, was used to determine whether a child met the *DSM* criteria for GID^{10,11} (for a detailed description of the clinical procedure and instruments, see Reference 21). The diagnosis was made by either a clinical child psychologist or a child and adolescent psychiatrist. IQ was assessed with Dutch versions of the Wechsler Preschool and Primary Scales of Intelligence¹⁷ or one of two versions of WISC.^{18,19}

Gender Identity/Gender Dysphoria. Table 2 provides the study design. At T_0 , a Dutch translation of the semistructured GIIC of Zucker et al.²³ was used. This child informant instrument consists of 12 items and measures two factors: affective gender confusion and cognitive gender confusion. Higher scores reflect more gender-atypical responses. Each question is scored on a three-point scale ranging from 0 to 2. A score of 0 is assigned if the child answers a factual question correctly (e.g., "Are you a boy or a girl?") or gives a putatively normal or stereotypic response (e.g., "no" to the question, "In your mind, do you ever think that you would like to be a [opposite sex]?"). A score of 1 is assigned if the child provides an ambiguous or intermediate response (e.g., "I don't know" to the question, "Do you think it is better to be a boy or a girl?"; "sometimes" to the question, "In your mind, do you ever think that you would like to be a [opposite sex]?"). A score of 2 is assigned to responses that are putatively atypical and without ambiguity (e.g., "yes" to the question, "In your mind, do you ever think that you would like to be a [opposite sex]?"). The GIIC strongly discriminated gender-referred children from controls, with a large effect size, using Cohen d of 1.72 for Canadian probands and of 2.98 for Dutch probands (M.S.C. Wallien, unpublished data, 2007).

At T_1 , a Dutch translation of the semistructured Gender Identity Interview for Adolescents and Adults (GIIAA) was used.²⁴ This interview has 27 items measuring gender identity and gender

TABLE 2
Study Design

Time	Group	Age, y	Instruments	Variable
T_0	All ($N = 77$)	5–12	GIIC	Gender
			GIQC	Gender
			CBCL	Psychological functioning
T_1	Persistence group ($n = 21$)	16–24	UGS	Gender
			BIS	Body satisfaction
T_1	Desistance group ($n = 23$)	16–28	Sexual orientation questionnaire	Sexual orientation
			GIIAA	Gender
			UGS	Gender
			BIS	Body satisfaction
T_1	Parent group ($n = 10$)	16–25	Parent questionnaire	Gender and sexual orientation

Note: GIIC = Gender Identity Interview for Children; GIQC = Gender Identity Questionnaire for Children; CBCL = Child Behavior Checklist; UGS = Utrecht Gender Dysphoria Scale; BIS = Body Image Scale; GIIAA = Gender Identity Interview for Adolescents and Adults.

dysphoria in adolescents and adults. Responses, rated on a five-point scale, are based on a time frame of the past 12 months. Lower scores reflect more gender-atypical responses. The GIHA score is calculated by summing scores on the completed items and dividing by the number of marked responses. Deogracias et al.²⁴ reported a Cronbach α of .97 and found that people with GID reported significantly more gender dysphoria than both heterosexual and nonheterosexual non-gender-dysphoric individuals, indicating good discriminant validity. Using a cutoff score of 3.00, they found that the sensitivity was 90.4% for the gender-dysphoric group and the specificity was 99.7% for the controls.

Gender Identity Questionnaire for Children. The GIQC is a one-factor, 14-item parent-report questionnaire covering a range of sex-typed behaviors that correspond to various features of the core phenomenology of the GID diagnosis. Each item is rated on a five-point scale for frequency of occurrence, with lower scores reflecting more cross-gendered behavior.²⁵ A GIQC score is calculated by summing the 14 items and then dividing the sum by 14. Johnson et al.²⁵ reported that a one-factor solution best fit the data, accounting for 43% of the variance, and that 14 of the 16 items have factor loadings 0.30 or greater. The GIQC strongly discriminated gender-referred children from controls, with a large effect size, using Cohen d of 3.70. With a specificity set at 95% for the controls, the sensitivity for the probands was 86.8%.

Utrecht Gender Dysphoria Scale (UGS). The UGS measures the degree of gender dysphoria in adolescents or adults.²⁶ Reported Cronbach α 's are .61 and .81 for male and female controls, .80 and .92 for males with gender dysphoria, and .78 and .80 for females with gender dysphoria. The scale showed good discriminant validity in a sample of individuals with and without GID and in gender-dysphoric individuals who were accepted and rejected for sex reassignment.²⁷ The scale consists of 12 items; scores range from 1 to 5, with higher scores reflecting more gender dysphoria.

Body Image Scale (BIS). The BIS,²⁸ used in a Dutch translation,²⁹ measures body satisfaction. On a five-point scale, one has to indicate satisfaction on 30 body parts and features (e.g., "neutral" body parts, such as hands or nose, and various primary and secondary sex characteristics). A score of 1 indicates the highest satisfaction regarding the specific body part; a score of 5 indicates the highest dissatisfaction.

Sexual Orientation. To assess sexual orientation, we used a questionnaire with nine items. The Sexual Orientation Questionnaire can be found in the supplemental digital content (online-only) materials at <http://links.lww.com/A569>. We assessed sexual orientation in four domains: sexual identity, sexual behavior (experience), sexual fantasy, and sexual attraction. In each of the domains, the questions were rated on a seven-point scale ranging from exclusively heterosexual (0) to exclusively homosexual (6).³⁰ Items 1 and 2 were used to rate sexual attraction, items 3 and 4 were used for the assessment of sexual fantasy, items 5 to 8 assessed sexual behavior, and item 9 pertained to sexual identity.

Psychological Functioning. To assess whether the desistance group was representative of all children who do not seek sex reassignment, and to check whether the parent group and desistance group were comparable with regard to psychological functioning, we used the Dutch translation of the CBCL.^{31,32} This instrument measures behavioral and emotional problems. Parents (or other caregivers) have to rate the child/young adult using a three-point scale: 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. Depending on age group and sex, Cronbach α 's for the internalizing, externalizing, and total score scales range from .78 to .93.

Psychosexual Outcome (Parent Report). This questionnaire consists of nine questions covering gender identity and sexual orientation of the participant, as observed by the parent. This instrument was used only if participants were not available for assessment at follow-up.

Procedure

Childhood Assessment (T_0). Childhood measures were collected as part of the child's clinical assessment at the Gender Identity Clinic. Four of the obtained measures were used: the CBCL, total IQ, the GIQC, and the GIIC. Background information was also collected during clinical assessment.

Follow-up (T_1). All children in the persistence group had applied for sex reassignment at the Gender Identity Clinic before the age of 16 and had followed the clinic's standardized diagnostic procedure.²¹ The assessment of the persisters took place during this procedure. All had subsequently been treated with GnRH analogs to suppress puberty and with cross-sex hormones after the age of 16 years. At our clinic, GnRH analogs are used as an aide in the diagnostic procedure (for a description of the eligibility criteria, see Reference 13).

The other adolescents received a letter in which the purpose of the study was explained. Although many participants were older than 18 years, we contacted the parents first and asked their permission to contact their child. We did so because the last clinical contact had been with them rather than with the child, and we did not want to approach their children without their consent. If the parents gave their permission, and the adolescent wanted to participate, we visited the participants at home. If the adolescent did not want to participate, we asked if they would allow their parents to fill out a questionnaire, the Parent Questionnaire on Psychosexual Outcome.

Two measures, UGS and BIS, were obtained from both the adolescents who were visited at home and the adolescents who were seen at the clinic because of their persistent gender dysphoria. In addition, the GIHA and the sexual orientation questionnaire were administered to the participants who were seen at home. Information on sexual orientation of the participants who applied for sex reassignment was gathered during the clinical procedure. Questions were part of a semistructured clinical interview.

The ethical committees of the University Medical Center Utrecht and VU University Medical Center approved the study.

RESULTS

T_0 : Childhood Gender Dysphoria

The percentages of DSM GID or GID NOS diagnoses were significantly different between the persistence and the desistance groups ($\chi^2_2 = 10.90$, $p = .004$) and between the persistence and the nonresponder groups ($\chi^2_1 = 7.6$, $p = .006$). All participants in the persistence group were given a diagnosis of GID. This was not the case in the other two groups (Table 1). When all nonpersisting groups were taken together, 69% had a GID diagnosis.

For the boys, the percentages of DSM GID or GID NOS diagnoses were also significantly different between the persistence and the desistance groups ($\chi^2_2 = 6.50$, $p = .011$). There were no significant differences between

TABLE 3Mean Scores on the Gender Identity Interview for Children and the Gender Identity Questionnaire at T₀

Scale	Persistence, Mean (SD)		Desistance, Mean (SD)		Nonresponders, Mean (SD)		Desistance- Persistence, <i>p</i>		Desistance- Nonresponders, <i>p</i>		Nonresponders- Persistence, <i>p</i>	
	Boys (<i>n</i> = 12)	Girls (<i>n</i> = 9)	Boys (<i>n</i> = 19)	Girls (<i>n</i> = 4)	Boys (<i>n</i> = 19)	Girls (<i>n</i> = 4)	Boys	Girls	Boys	Girls	Boys	Girls
	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>						
GIIC	<i>n</i> = 9	<i>n</i> = 8	<i>n</i> = 19	<i>n</i> = 3	<i>n</i> = 18	<i>n</i> = 3	.02	NS	NS	NS	NS	.02
	11.6 (4.6)	12.9 (1.8)	7.2 (4.7)	11.3 (5.5)	9.3 (5.4)	6.7 (4.5)						
GIQC	<i>n</i> = 11	<i>n</i> = 7	<i>n</i> = 19	<i>n</i> = 4	<i>n</i> = 16	<i>n</i> = 3	.008	NS	NS	NS	0.02	.03
	2.1 (0.4)	2.2 (0.6)	2.6 (0.6)	2.9 (0.4)	2.6 (0.7)	3.2 (0.4)						

Note: GIIC = Gender Identity Interview for Children; GIQC = Gender Identity Questionnaire for Children; NS = not statistically significant.

the desistance and the nonresponder groups, or between the persistence and the nonresponder groups. Among the girls, the percentages of *DSM* diagnoses of GID or GID NOS were significantly different between the persisting and the nonresponding girls ($\chi^2_1 = 8.775, p = .003$), but not between the persisting and desisting girls (Table 1).

With regard to the scores on the GIIC and GIQC, persisters generally showed more cross-gender behavior than the other groups. The persistence group had a significantly higher mean GIIC score (mean 12.2) than the desistance group (mean 7.6; $z = -2.35, p = .02$) and the nonresponder group (mean 8.9; $z = -2.01, p = .04$). This indicates more cross-gender identification in the total persistence group than in the desistance group (Table 3). The persisters had a significantly lower mean GIQC score than the desisters ($z = -2.782, p = .005$) and the nonresponders ($z = -2.82, p = .005$), again reflecting more cross-gender identification in childhood

in the persistence group than in the desistance and the nonresponder groups.

Among the boys, the scores on both the GIIC and the GIQC indicated that the persisting subgroup had a more cross-gender identification and that the persisters showed a more cross-gender behavior in childhood than the desisting boys. Among the girls, the scores on both the GIIC and the GIQC indicated that the persisting girls had a more cross-gender identification and showed more cross-gender behavior than the nonresponding girls but not the desisting girls (Table 3).

T₁: Gender Dysphoria

At T₁, all participants in the persistence group had been given a *DSM* diagnosis of GID. The desistance group did not have a second clinical assessment, but their mean GIIC scores (1.1) and their UGS scores indicated that they no longer had gender-dysphoric

TABLE 4Mean Scores on the Gender Identity Interview for Adolescents and Adults and on the Utrecht Gender Dysphoria Scale and the Body Image Scale at T₁

Scale	Persistence			Desistance			Persistence- Desistance, <i>p</i>		
	All	Boys	Girls	All	Boys	Girls	All	Boys	Girls
GIIC									
Divided score, mean (SD)				<i>n</i> = 17	<i>n</i> = 3				
				1.2 (0.2)	1.1 (0.2)				
Total score, mean (SD)				31.8 (4.8)	30.1 (6.4)				
UGS	<i>n</i> = 12	<i>n</i> = 5	<i>n</i> = 7	<i>n</i> = 1	<i>n</i> = 19	<i>n</i> = 2			
Total score, mean (SD)	53.5 (7.4)	50.6 (10.6)	55.6 (3.8)	13.6 (3.0)	13.6 (3.1)	13.0 (1.4)	.001	.001	.004
BIS	<i>n</i> = 16	<i>n</i> = 9	<i>n</i> = 7	<i>n</i> = 17	<i>n</i> = 14	<i>n</i> = 3			
Total score, mean (SD)	3.1 (0.4)	3.1 (0.4)	3.1 (0.5)	2.5 (0.5)	2.4 (0.3)	2.5 (1.0)	.001	.001	NS

Note: Desistance group consists of children who had not applied for sex reassignment when approached by us at 16 years or older. Persistence group consists of children who were still gender dysphoric at 16 years or older. Values are cited in italics. GIIC = Gender Identity Interview for Adolescents and Adults; UGS = Utrecht Gender Dysphoria Scale; BIS = Body Image Scale; NS = not statistically significant.

feelings at follow-up (Table 4). With regard to the UGS, it was found that the persistence group had significantly more gender dysphoria than the desistance group ($z = -4.81$, $p = .001$; Table 4). This was also found when separately analyzed for boys and girls (boys: $z = -3.51$, $p = .001$; girls: $z = -2.06$, $p = .004$).

As expected, the persistence group also reported significantly more body dissatisfaction on the BIS ($z = -3.62$, $p = .001$; Table 4) than the participants in the desistance group. The desistance group reported, on average, dissatisfaction with four body parts, and the participants in the persistence group reported, on average, dissatisfaction with nine body parts. Most participants in the persistence group were dissatisfied with their primary and secondary sex characteristics and height. Most of the subjects in the desistance group were dissatisfied with "sex neutral" body characteristics such as nose, shoulders, or feet, and they were satisfied with their primary sex characteristics. Analyzed separately for the sexes, the persisting boys reported more body dissatisfaction than the desisting boys ($z = -3.5$, $p = .001$), whereas this was not found for the girls.

T₁: Sexual Orientation

Table 5 shows the data on sexual orientation at follow-up. Participants were classified in the following way, according to their scores on sexual fantasy, sexual

attraction, and sexual behavior: heterosexual (Kinsey rating 0–1), bisexual (Kinsey rating 2–4), and homosexual (Kinsey rating 5–6).³⁰ The participants also rated their sexual identity as heterosexual, bisexual, or homosexual. In the parent group, only the parents' ideas about their children's sexual attraction feelings could be asked for. We therefore have more participants who are rated on the sexual attraction dimension than on the other sexual orientation dimensions.

On the sexual attraction dimension, about half of the boys ($n = 25$) in the desistance group were attracted to men ($n = 14$), and the others ($n = 11$) were attracted to women. Almost all natal boys in the persistence group ($n = 11$) were attracted to men; only one natal boy reported to be attracted to women. All persisting girls were attracted to women, and all desisting girls were attracted to men.

On the sexual identity dimension, half of the boys in the desistance group reported having a homosexual identity, three boys reported a bisexual identity, and one-third reported a heterosexual identity. All desisting girls reported having a heterosexual identity. Because we classified sexual orientation in relation to birth sex, all natal boys and almost all natal girls in the persistence group reported a homosexual identity. Only one natal girl in the persistence group classified herself as bisexual, although she reported that she was attracted to girls.

TABLE 5

Percentage Participants Who Rated Themselves on Three Dimensions of Sexual Orientation and on Sexual Identity

Group	Attraction		Behavior		Fantasy		Sexual Identity	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Desistance	$n = 25$	$n = 3$	$n = 13$	$n = 2$	$n = 16$	$n = 1$	$n = 18$	$n = 3$
Heterosexual	44	100	23	100	19	100	27	100
Bisexual	0	0	23	0	25	0	17	0
Homosexual	56	0	54	0	56	0	56	0
Persistence	$n = 12$	$n = 7$	$n = 6$	$n = 3$	$n = 5$	$n = 2$	$n = 9$	$n = 8$
Heterosexual	8	0	17	0	17	0	0	0
Bisexual	0	0	0	0	0	0	0	12
Homosexual	92	100	83	100	83	100	100	88
Combined group of gender-dysphoric children	$n = 37$	$n = 10$	$n = 19$	$n = 5$	$n = 21$	$n = 3$	$n = 27$	$n = 11$
Heterosexual	32	30	21	40	19	0	19	18
Bisexual	0	0	16	0	19	33	19	9
Homosexual	68	70	63	60	62	66	62	73
Normative study	$n = 1,628$	$n = 1,676$	$n = 1,618$	$n = 1,670$	$n = 1,624$	$n = 1,674$		
Heterosexual	96	98	94	83	91	76		
Homosexual	3	1	6	17	9	24		

Note: The percentages are in relation to birth sex. In the combined group, the percentages of children in the Persistence and the Desistance groups are combined. The normative data are from a study by de Graaf et al.³³

We also compared our sexual orientation findings with prevalence estimates from a large Dutch study among 3,304 adolescents and young adults (age range 12–25 years).³³ Table 5 shows that, in all our groups, there were considerably more adolescents with a nonheterosexual sexual orientation than in the non-referred Dutch adolescents. In our study group, the overall odds of reporting same-sex or bisexual attraction was 2.1 (32 of the 47 children reported same-sex attraction, and 15 were attracted to the opposite sex: $32/15 = 2.1$; for the natal males, it was 2.1; for the natal females, 2.3). This percentage would even be higher if one assumes that most nonresponders may also have a homosexual sexual orientation. Adult individuals with childhood gender dysphoria are thus much more likely to have a nonheterosexual sexual orientation than a heterosexual sexual orientation. In the normative study, the odds of same-sex or bisexual attraction was 0.02 (68 of the 3,268 children reported same-sex or bisexual attraction; for the males, it was 0.03; for the females, 0.04). This implies that it is about 100 times more likely that someone with childhood gender dysphoria is attracted to partners of the same sex or to both sexes than someone without a gender-dysphoric history.

Participants (both persisters and desisters) who were rated differently on the Kinsey dimensions did not differ in age at T_0 or at T_1 . There was one significant difference between the GIQC score of the participants with same-sex or bisexual attraction and the participants with a heterosexual attraction ($z = -2.53, p = .01$). The participants with same-sex or bisexual attraction had a lower score (mean 2.26) than the participants with a heterosexual attraction (mean 2.78). This indicates more parent-reported gender atypicality in childhood in participants with same-sex or bisexual attraction than in participants with a heterosexual attraction. However, when we analyzed the GIQC scores of participants in the desistance group only, we found no significant differences between the participants with same-sex or bisexual attraction and the participants with heterosexual attraction. Therefore, the more extreme scores of the persisters were responsible for the total group difference on the GIQC.

DISCUSSION

This study investigated the psychosexual outcome among gender-dysphoric children and determined

whether childhood characteristics gave an indication of later GID. We found that 27% of our total group of gender-dysphoric children was still gender dysphoric in adolescence. In the Netherlands, treatment is covered by insurance and easily available, but only in the Amsterdam clinic. It therefore seems unlikely that some nonresponders are, in fact, persisters, and that the observed persistence rate of 27% differs much from the actual persistence rate.

For boys, our percentage of persisting gender dysphoria was similar to what Zucker and Bradley⁸ reported: one of five boys was still gender dysphoric in adolescence/young adulthood. For girls, we found a much higher percentage of persisters than was found in the only follow-up study on girls by Drummond et al.¹⁶ In our study, 50% of the gender-dysphoric girls seemed to be persisters, whereas Drummond et al.¹⁶ found that only 12% of gender-dysphoric girls seemed to have persistent gender dysphoria. Our higher rate of persisting girls could perhaps be explained by differences in childhood cross-gender behavior between the Canadian and Dutch referred children. Although no direct comparison between the girls in the Drummond et al.¹⁶ study and our follow-up study could be made with respect to their scores on the GIIC, a study comparing 376 Canadian and 228 Dutch gender-referred children from both centers reported that the Dutch girls scored significantly higher on the GIIC than the Canadian girls (M.S.C. Wallien, unpublished data, 2007). However, the percentages of girls fulfilling the childhood GID criteria in the study of Drummond et al. (64%) and our study (77%) were not significantly different. In another study, it was found that Dutch children are, on average, referred for gender problems at an older age than Canadian children.³⁴ It may thus be that a combination of a relatively late age at referral and severity of gender-dysphoria accounts for the differences between the rates of female persisters in the two studies. Because these are reports from only two studies with relatively small numbers of female participants, it is, of course, possible that the percentages of females with persisting gender dysphoria will change when larger samples are studied.

We also found that both boys and girls with more extreme gender dysphoria were more likely to develop adolescent/adult GID, whereas children with less extreme gender dysphoria seemed to have overcome their gender dysphoria. For example, all participants in

the persistence group were given a complete GID diagnosis in childhood, whereas half of the group of desisting children was subthreshold for the diagnosis (Table 1). The diagnoses were partly based on a number of parent and child measures (GIIC and GIQC scores), and scores on these instruments also fairly consistently indicated that the persisters showed more childhood gender atypicality than the desisters. Comparing the scores separately for the sexes, similar results were found, although not all comparisons were significant. However, this may have been due to the sometimes small numbers in the various subgroups. Taking all results together, it seems that certain childhood gender identity and gender role measures may give an indication of gender dysphoria persistence after puberty. Clinicians should therefore take child and parent reports of cross-gender identification and behavior seriously, to address them in a timely manner when the subjects enter adolescence. It is conceivable that, in the future, persisting children will be identified and treated with GnRH analogs, even before the actual beginning of puberty. However, at the moment, their reaction to the first physical signs of puberty is still used diagnostically. Clearly, many more studies are needed before one can make any evidence-based recommendations about hormonal interventions in prepubertal children.

With regard to sexual orientation, almost all persisters seemed to be attracted to someone of the same biological sex at follow-up, whereas in the desistance group, this was found for only about half of the participants. In total (persistence and desistance groups together), two-thirds of the participants reported having a same-sex or bisexual attraction. This high percentage of nonheterosexuality is similar to what has been reported in other follow-up studies.¹⁻⁸ Compared with sexual orientation rates from a Dutch normative study, both our boys and girls were far more likely to have a bisexual or homosexual sexual orientation. Childhood gender dysphoria thus seems to be associated with a high rate of later same-sex or bisexual sexual orientation. In clinical practice, gender-dysphoric children and their parents should be made aware of such an outcome and, if this would create problems, be adequately counseled.

Because almost all persisters reported having same-sex sexual attractions, there were no sex differences in this group. However, in the desistance group, half of the boys reported a homosexual or bisexual sexual orienta-

tion, whereas none of the desisting girls did. In contrast to our findings, Drummond et al.¹⁶ found much higher rates of desisting girls with either a homosexual or bisexual sexual orientation. Their rates for either a homosexual or bisexual sexual orientation in fantasy and behavior were 30% (6 of 20) and 26% (4 of 15). This difference can probably be attributed to the fact that our sample size of desisting girls was small ($n = 3$) and that two of our desisting girls (16 years of age) mentioned that they were still questioning their sexuality. If one of the two would, at an older age, seem to be homosexual, the numbers would be much more comparable. All of the desisting homosexual/bisexual girls in the study of Drummond et al.¹⁶ were older than 23. Thus, it is possible that these girls were more "crystallized" with respect to their sexual identities. A study by Diamond³⁵ showed that it is not uncommon for nonheterosexual adolescent girls to change their sexual orientation over time. In her 2-year follow-up study of 80 lesbian, bisexual, and "unlabeled" women, first interviewed at 16 to 23 years of age, half of the women seemed to change their sexual identities more than once, and one-third changed their sexual identity since the first interview. Changes in sexual attraction were small but were larger among bisexuals and "unlabeled" females. Considering this, it is possible that the apparent differences between our results and those of Drummond et al.¹⁶ are, in fact, nonexistent.

Research on the sexual identity development of lesbian, gay, and bisexual youths has shown that the sexual orientation, especially for bisexual youths, may change over time.^{36,37} Our results on sexual orientation also suggest that some male participants were still in an experimentation phase, as the percentage of participants reporting a heterosexual or bisexual orientation differs between the three dimensions of sexual orientation. Furthermore, social desirability is a key validity issue in the assessment of sexual orientation during the adolescent years. One limitation of this study is that we did not measure the participants' propensity to give socially desirable responses, because we did not want to lose cooperation by making the follow-up session unnecessarily long and tedious. Therefore, it is possible that some of our "heterosexual" adolescents were, in fact, attracted to people of the same sex. Even if this were not true, the prevalence rates of same-sex attraction in our study are still substantially higher than in the general population.

Carver et al.³⁸ assumed that gender atypicality may precede the development of a homosexual identity as such. Drummond et al.¹⁶ indeed found that the participants with a bisexual or homosexual orientation recalled more cross-gender behavior during childhood than the participants with a heterosexual or asexual sexual orientation. Although our persisting and desisting participants taken together with a homosexual or bisexual sexual orientation were more cross-gendered in childhood than the participants with a heterosexual sexual orientation, we did not find any significant differences on the childhood measurements between the desisting participants with different sexual orientation outcomes. It is, however, possible that our results did not reach statistical significance because of the small sample sizes. Conversely, in retrospective reports, there is always a risk of memory distortion. It is clear that long-term prospective follow-up studies, in which gender nonconformity is measured in large normative samples of young children, and psychosexual outcome in adolescence or adulthood, are needed to gain more insight in the relationship between childhood gender nonconformity and sexual orientation.

In response to our question at what point in time the desisting participants noticed that their cross-gender preferences and feelings had decreased or disappeared, most answered that the change took place upon entry into secondary school. Only few answered that it took place during the first stages of puberty. It is understandable that an intensification or moderation of the gender dysphoria is closely related to the development of the physical markers of maleness and femaleness. Why most participants reported entrance into secondary school as a “turning point” is less clear. It may be that secondary school entrance is better remembered than the start of puberty because puberty concerns a more gradual transition. More systematic follow-up every few years, especially around critical developmental time points (i.e., school entry, pubescent milestones such as menarche or first ejaculation), is needed to know better exactly when and how GID persistence or desistance takes place.³⁹

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REFERENCES

1. Bakwin H. Deviant gender-role behavior in children: relation to homosexuality. *Pediatrics*. 1968;41:620–629.

2. Davenport CW. A follow-up study of 10 feminine boys. *Arch Sex Behav*. 1986;15:511–517.
3. Green R. *The “Sissy Boy Syndrome” and the Development of Homosexuality*. New Haven, CT: Yale University Press; 1987.
4. Kosky RJ. Gender-disordered children: does inpatient treatment help? *Med J Aust*. 1987;146:565–569.
5. Lebovitz PS. Feminine behavior in boys: aspects of its outcome. *Am J Psychiatry*. 1972;128:1283–1289.
6. Money J, Russo AJ. Homosexual outcome of discordant gender identity/role in childhood: longitudinal follow-up. *J Pediatr Psychol*. 1979;4:29–41.
7. Zuger B. Early effeminate behavior in boys: outcome and significance for homosexuality. *J Nerv Ment Dis*. 1984;172:90–97.
8. Zucker KJ, Bradley SJ. *Gender Identity Disorder and Psychosexual Problems in Children and Adolescents*. New York: Guilford Press; 1995.
9. Cohen-Kettenis PT. Letter to the editor: gender identity disorder in the DSM? *J Am Acad Child Adolesc Psychiatry*. 2001;40:391.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed*. Washington, DC: American Psychiatric Association; 1994.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Revised Text*. Washington, DC: American Psychiatric Association; 2001.
12. Hill DB, Rozanski C, Carfagnini J, et al. Gender identity disorders in childhood and adolescence: a critical inquiry. *Int J Sex Health*. 2007;19:57–75.
13. Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and pediatric endocrinology aspects. *Eur J Endocrinol*. 2006;155:S131–S137.
14. Green R, Roberts CW, Williams K, Goodman M, Mixon A. Specific cross-gender behaviour in boyhood and later homosexual orientation. *Br J Psychiatry*. 1987;15:84–88.
15. Bailey JM, Zucker KJ. Childhood sex-typed behavior and sexual orientation: a conceptual analysis and quantitative review. *Dev Psychol*. 1995;31:43–55.
16. Drummond KD, Bradley SJ, Peterson-Badali M, Zucker KJ. A follow-up study of girls with gender identity disorder. *Dev Psychol*. 2008;44:34–45.
17. Wechsler D. *Wechsler Preschool and Primary Scales of Intelligence (WPPSI-R)*. 1997. Flemish-Dutch translation by G. Vandersteene and A. Bos.
18. Wechsler D. *Wechsler Intelligence Scale for Children: Manual*, 3rd ed. San Antonio, TX: The Psychological Corporation; 1991.
19. Wechsler D. *Wechsler Intelligence Scale for Children: Manual*, 3rd ed. Dutch translation by W. Kort, M. Schittekatte, P.H. Dekker, P. Verhaeghe, E.L. Compaan, lic. M. Bosmans, lic. G. Vermeir; 2005.
20. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
21. Cohen-Kettenis PT. Gender identity disorder. In: Gillberg C, Harrington R, Steinhausen HC, eds. *A Clinician’s Handbook of Child and Adolescent Psychiatry*. Cambridge: Cambridge University Press; 2006:695–725.
22. Verhulst FC, Van der Ende J, Koot HM. *Manual for the Teacher’s Report Form (TRF)*. Rotterdam: Erasmus University/Department of Child and Adolescent Psychiatry, Sophia Children’s Hospital; 1997.
23. Zucker KJ, Bradley SJ, Lowry Sullivan CB, Kuksis M, Birkenfeld-Adams A, Mitchell JN. A gender identity interview for children. *J Pers Assess*. 1993;61:443–456.
24. Deogracias JJ, Johnson LL, Meyer-Bahlburg HFL, Kessler SJ, Schober JM, Zucker KJ. The gender identity/gender dysphoria questionnaire for adolescents and adults. *J Sex Res*. 2007;4:370–379.
25. Johnson LL, Bradley SJ, Birkenfeld-Adams AS, et al. A parent-report gender identity questionnaire for children. *Arch Sex Behav*. 2004;33:105–116.
26. Doorn CD, Kuiper AL, Verschoor AM, Cohen-Kettenis PT. Het verloop van de geslachtsaanpassing: een 5-jarige prospectieve studie [The course of sex reassignment: a 5-year prospective study]. Report for the Dutch National Health Council; 1996.
27. Cohen-Kettenis PT, van Goozen SHM. Sex reassignment of adolescent

- transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997;36:263–271.
28. Lindgren TW, Pauly IB. A Body Image Scale for evaluating transsexuals. *Arch Sex Behav*. 1975;4:639–656.
 29. Kuiper AJ. *Transseksualiteit: Evaluatie van de Geslachtsaanpassende Behandeling [Transsexuality: Evaluation of Sex-Reassignment]*. Amsterdam: VU University Press; 1991.
 30. Kinsey AC, Pomeroy WB, Martin CE. *Sexual Behavior in the Human Male*. Philadelphia: WB Saunders; 1948.
 31. Achenbach TM. *Manual for the Child Behavior Checklist and 1991 Profile*. Burlington: University of Vermont Department of Psychiatry; 1991.
 32. Verhulst FC, van der Ende J, Koot H. *Handleiding voor de CBCL/4-18*. Rotterdam: University Press; 1996.
 33. de Graaf H, Meijer S, Poelman J, Vanwesenbeeck I. *Seks onder je 25e: Seksuele gezondheid van jongeren in Nederland anno 2005 [Sex Under 25: Sexual Health of Youth in the Netherlands Anno 2005]*. Delft: Eburon; 2005.
 34. Cohen-Kettenis PT, Owen A, Kaijser VG, Bradley SJ, Zucker KJ. Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: a cross-national, cross-clinic comparative analysis. *J Abnorm Child Psychol*. 2003;31:41–53.
 35. Diamond LM. Sexual identity, attraction, and behavior among young sexual-minority women over a 2-year period. *Dev Psychol*. 2000;36:241–250.
 36. Rosario M, Schrimshaw EW, Hunter J, Braun L. Sexual identity development among lesbian, gay, and bisexual youths: consistency and change over time. *J Sex Res*. 2006;43:46–58.
 37. Stokes JP, Damon W, McKirnan DJ. Predictors of movement towards homosexuality: a longitudinal study of bisexual men. *J Sex Res*. 1997;34:304–312.
 38. Carver PR, Egan SK, Perry DG. Children who question their heterosexuality. *Dev Psychol*. 2004;40:43–53.
 39. Wallien MSC, Cohen-Kettenis PT, Lambert SL, Owen-Anderson A, Bradley SJ, Zucker KJ. Cross-National Replication of the Gender Identity Interview for Children, submitted.

Prospective Effects of Attention-Deficit/Hyperactivity Disorder, Conduct Disorder, and Sex on Adolescent Substance Use and Abuse Elkins IJ, McGue M, Iacono WG

Context: Attention-deficit/hyperactivity disorder (ADHD), an early manifestation of externalizing behavior, may identify children at high risk for later substance abuse. However, the ADHD-substance abuse relationship often disappears when co-occurring conduct disorder (CD) is considered. **Objective:** To determine whether there is a prospective relationship between ADHD and the initiation of substance use and disorders, and whether this relationship depends on the ADHD subtype (hyperactive/impulsive or inattentive), CD, or sex. **Design, Setting, and Participants:** Dimensional and categorical measures of ADHD and CD were examined via logistic regression analyses in relation to subsequent initiation of tobacco, alcohol, and illicit drug use by 14 years of age and onset of substance use disorders by 18 years of age in a population-based sample of 11-year-old twins (760 female and 752 male twins) from the Minnesota Twin Family Study. **Main Outcome Measures:** Structured interviews were administered to adolescents and their mothers regarding substance use and to generate diagnoses. **Results:** For boys and girls, hyperactivity/impulsivity predicted initiation of all types of substance use, nicotine dependence, and cannabis abuse/dependence (for all, $p < .05$), even when controlling for CD at 2 time points. By contrast, relationships between inattention and substance outcomes disappeared when hyperactivity/impulsivity and CD were controlled for, with the possible exception of nicotine dependence. A categorical diagnosis of ADHD significantly predicted tobacco and illicit drug use only (adjusted odds ratios, 2.01 and 2.82, respectively). A diagnosis of CD between 11 and 14 years of age was a powerful predictor of substance disorders by 18 years of age (all odds ratios, 94.27). **Conclusions:** Hyperactivity/impulsivity predicts later substance problems, even after growth in later-emerging CD is considered, whereas inattention alone poses less risk. Even a single symptom of ADHD or CD is associated with increased risk. Failure in previous research to consistently observe relationships between ADHD and substance use and abuse outcomes could be due to reliance on less-sensitive categorical diagnoses. Reproduced with permission from *Archives of General Psychiatry*, 2007;64(10): 1145–1152. Copyright © 2007, American Medical Association. All rights reserved.

EXHIBIT G

44

Gender Identity Disorder

Kenneth J. Zucker

Introduction

This chapter provides an overview of seven aspects of our knowledge about gender identity disorder (GID) in children and adolescents:

- 1 phenomenology;
- 2 epidemiology;
- 3 diagnosis and assessment;
- 4 associated psychopathology;
- 5 aetiology;
- 6 long-term follow-up; and
- 7 treatment.

Terminology

Six terms that will be used throughout are briefly described. These are:

- 1 sex;
- 2 gender;
- 3 gender identity;
- 4 gender role (masculinity–femininity);
- 5 sexual orientation; and
- 6 sexual identity.

Sex

Sex refers to attributes that collectively, and usually harmoniously, characterize biological maleness and femaleness. In humans, the most well-known attributes that constitute biological sex include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, the internal reproductive structures, and the external genitalia (Migeon & Wisniewski 1998). Over the past couple of decades, there has also been great interest in the possibility that the human brain has certain sex-dimorphic neuroanatomical structures which, perhaps, emerge during the process of prenatal physical sex differentiation (for recent developments in understanding aspects of biological sex, see Haqq & Donahoe 1998; Vilain & McCabe 1998).

Gender

Gender is often used to refer to psychological or behavioural characteristics associated with males and females (Ruble &

Martin 1998). The use of gender as a technical term is a recent phenomenon. As late as the mid-1950s, it was not even part of the professional literature that purported to study psychological similarities and differences between males and females. In fact, the first term introduced to the literature was that of *gender role*, not gender (Money 1955).

Over the past 40 years, three major developments have occurred with regard to the usage of the terms ‘sex’ and ‘gender’. First, there has been a tendency to conflate the use of the two terms, so that it is not always clear if one is referring to biological or psychological characteristics that distinguish males from females (Gentile 1993). Secondly, the use of the terms ‘sex’ and ‘gender’ has been related to assumptions about causality, in that the former is used to refer exclusively to biological processes and the latter is used to refer exclusively to psychological or sociological processes (for critiques of this division, see Money 1985; Maccoby 1988). As a result, some researchers who study humans employ such terms as *sex-typical*, *sex-dimorphic*, and *sex-typed* to characterize sex differences in behaviour, because terms of this kind are descriptively more neutral with regard to putative aetiology. The third development, as noted by Zucker & Bradley (1995), is that Money’s original use of the term ‘gender role’ has been decomposed into three conceptually distinct component parts that are identified by the terms ‘gender identity’, ‘gender role’ and ‘sexual orientation’.

Gender identity

Gender identity was introduced into the professional lexicon by Hooker and by Stoller in the early 1960s (Money 1985). Stoller (1964, p. 453) used the slightly different term *core gender identity* to describe a young child’s developing ‘fundamental sense of belonging to one sex’. This term was later adopted by cognitive-developmental psychologists, such as Kohlberg (1966), who defined gender identity as the child’s ability to discriminate accurately males from females and then to identify his or her own gender status correctly—a task considered by some to be the first ‘stage’ in ‘gender constancy’ development, the end state of which is the knowledge of gender invariance (Kohlberg 1966; Eaton & Von Bargen 1981).

Gender role

Gender role has been used extensively by developmental psychologists to refer to behaviours, attitudes and personality traits

that a society, in a given culture and historical period, designates as masculine or feminine, i.e. those more ‘appropriate’ to, or typical of, the male or female social role (Ruble & Martin 1998). It should be remembered that defining gender roles in this way assumes that they are completely arbitrary and social in origin, a view not universally shared by researchers in the field. In any case, from a descriptive point of view, the measurement of gender role behaviour in young children includes several easily observable phenomena, including affiliative preference for same-sex vs. opposite-sex peers, roles in fantasy play, toy interests, dress-up play, and interest in rough-and-tumble play. In older children, gender role has also been measured using personality attributes with stereotypic masculine or feminine connotations (Ruble & Martin 1998).

Sexual orientation

Sexual orientation is defined by a person’s relative responsiveness to sexual stimuli. The most salient dimension of sexual orientation is probably the sex of the person to whom one is attracted sexually. This stimulus class is obviously how one defines a person’s sexual orientation, or erotic partner preference, as heterosexual, bisexual or homosexual. In contemporary sexology, sexual orientation is often assessed by psychophysiological techniques, such as penile plethysmography or vaginal photoplethysmography (Rosen & Beck 1988), although structured interview assessments have become increasingly common, particularly when respondents do not have a compelling reason to conceal their sexual orientation.

Sexual identity

It is important to uncouple the construct of sexual orientation from the construct of *sexual identity*. A person may, for example, be predominantly aroused by homosexual stimuli, yet not regard himself or herself as ‘a homosexual’, for whatever reason. Sociologists, particularly those of the ‘social scripting’ and ‘social constructionist’ schools, have articulated this notion most forcefully, arguing that the incorporation of sexual orientation into one’s sense of identity is a relatively recent phenomenon, culturally variable, and the result of a complex interplay of sociohistorical events (Gagnon 1990; Weeks 1991). Anthropologists, such as Herdt (1981), who have described ritualized age-structured homosexual behaviour in non-Western cultures, note that such behaviour is not at all tied to a homosexual sexual identity, but rather is a rite of passage to mature adult heterosexuality.

In contemporary Western culture, there are many individuals who are primarily or exclusively sexually responsive to same-sex persons, yet do not adopt a homosexual or ‘gay’ identity (Ross 1983). Moreover, there are also individuals who engage in extensive homosexual behaviour, yet who are not predominantly aroused by homosexual stimuli or do not consider themselves to ‘be’ homosexual, such as among male adolescents who have

sex with men for money. Thus, one must pay attention to the empirical evidence regarding disjunctions between sexual orientation and sexual identity (for a detailed analysis see Laumann *et al.* 1994).

Phenomenology

Boys and girls diagnosed with GID as described in the fourth edition of the Diagnostic and Statistical Manual (DSM-IV) (American Psychiatric Association 2000), or in ICD-10 (World Health Organization 1992), display an array of sex-typed behaviour signalling a strong psychological identification with the opposite sex. These behaviours include:

- 1 identity statements;
- 2 dress-up play;
- 3 toy play;
- 4 roles in fantasy play;
- 5 peer relations;
- 6 motoric and speech characteristics;
- 7 statements about sexual anatomy; and
- 8 involvement in rough-and-tumble play.

In general, there is a strong preference for sex-typed behaviours more characteristic of the opposite sex and a rejection or avoidance of sex-typed behaviours more characteristic of one’s own sex. There are also signs of distress and discomfort about one’s status as a boy or a girl, including verbal expressions of dislike or disgust about one’s genital anatomy. The behaviours that characterize GID in children occur in concert, not in isolation. It is this behavioural patterning that is of clinical significance, and recognition of the patterning is extremely important in conducting a diagnostic assessment.

The onset of most of the behaviours occurs during the preschool years (2–4 years), if not earlier. Clinical referral often occurs when parents begin to feel that the pattern of behaviour is no longer a ‘phase’, a common initial parental appraisal, that their child will ‘grow out of’ (Stoller 1967; Zucker 2000a). From a developmental perspective, the onset occurs during the same period that more typical sex-dimorphic behaviours can be observed in young children (Ruble & Martin 1998). For a more detailed account of phenomenology, see Green (1974) and Zucker & Bradley (1995).

Epidemiology

Prevalence

The prevalence of GID in children has not been formally studied by epidemiological methods. Nevertheless, Meyer-Bahlburg’s (1985) characterization of GID as a ‘rare phenomenon’ is not unreasonable. Prevalence estimates of GID in adults suggest an occurrence of 1 in 24 000–37 000 men and 1 in 103 000–150 000 women (Meyer-Bahlburg 1985). Subsequently, Bakker

et al. (1993) inferred the prevalence of adult GID in the Netherlands from the number of persons receiving ‘cross-gender’ hormonal treatment at the main adult gender identity clinic in that country: 1 in 11 000 men and 1 in 30 400 women.

However, this approach suffers from at least three limitations. First, it relies on the number of persons who attend specialty clinics serving as gateways for surgical and hormonal sex reassignment, which may not see all gender-dysphoric adults. Secondly, unlike adult females with gender dysphoria, who are almost always attracted sexually to biological females, adult males with GID are about equally likely to be attracted sexually to biological males or females (Blanchard *et al.* 1987). A childhood history of GID, or its subclinical manifestation, occurs largely among gender-dysphoric adults with a homosexual sexual orientation. Estimates of the prevalence of GID in childhood inferred from the prevalence of GID in adult males should take this into account. Thirdly, the assumption that GID in children will persist into adulthood is not necessarily true (see below). It is likely therefore that the prevalence of GID is higher in children than it is in adults.

Another approach to the estimate of prevalence can borrow from normative studies of children in whom specific cross-gender behaviours were assessed (Zucker 1985, pp. 87–95). One source of information comes from the widely used Child Behavior Checklist (CBCL; Achenbach & Edelbrock 1983), a parent-report behaviour problem questionnaire with excellent psychometric properties. It includes two items (out of 118) that pertain to cross-gender identification: ‘behaves like opposite sex’ and ‘wishes to be of opposite sex’. On the CBCL, ratings are made on a 3-point scale (0, not true; 1, somewhat or sometimes true; and 2, very true or often true). In the standardization study, endorsement of both items was more common for girls than for boys, regardless of age and clinical status (referred vs. non-referred).

As reported by Zucker *et al.* (1997a), among non-referred boys (ages 4–11 years), 3.8% received a rating of 1 and 1.0% a rating of 2 for the item ‘behaves like opposite sex’, but only 1.0% received a rating of 1 and 0.0% a rating of 2 for the item ‘wishes to be of opposite sex.’ The comparable percentages among non-referred girls was 8.3, 2.3, 2.5 and 1.0%, respectively. These findings suggest that there is a sex difference in the occurrence of mild displays of cross-gender behaviour, but not with regard to more extreme cross-gender behaviour. Similar results were obtained from the Achenbach, Connors, and Quay Behaviour Checklist (ACQ; Achenbach *et al.* 1991), which contains three items pertaining to cross-gender identification out of a total of 215 (two from the original CBCL and a third, ‘Dresses like or plays at being opposite sex’; for details see Zucker *et al.* 1997a).

The main problem with such data is that they do not adequately identify patterns of cross-gender behaviour that would be of use in determining ‘caseness.’ Thus, such data may be best

viewed as screening devices for more intensive evaluation (Pleak *et al.* 1989; Sandberg *et al.* 1993).

Incidence

Lothstein (1983) speculated, on clinical grounds, that parents who had been influenced by the cultural *Zeitgeist* to use ‘non-sexist’ socialization techniques may have inadvertently induced gender identity conflict in their children. However, there are no systematic data regarding changes, or the lack thereof, in the incidence of GID over the past several decades.

Sex differences in referral rates

Consistently, it has been observed that boys are referred more often than girls for concerns regarding gender identity. This has been reflected in both research and clinical reports of treatment. In our own clinic, Zucker *et al.* (1997a) reported a referral ratio of 6.6:1 ($n=275$) of boys to girls.

How might this disparity be best understood? One possibility is that the sex difference in referral rates reflects a true sex difference in prevalence. Another possibility is that social factors have a role in accounting for the disparity. For example, it is well established that parents, teachers and peers are less tolerant of cross-gender behaviour in boys than in girls (Fagot 1985), which might result in a sex-differential in clinical referral (for review see Zucker & Bradley 1995). Weisz & Weiss (1991) devised a ‘referability index’ (RI) which reflected the frequency with which a child problem, adjusted for its prevalence in the general population, resulted in a clinic referral. All 118 items from the CBCL were analysed in a comparison of clinic-referred and non-referred children. Among parents in the USA, the 20 most referable problems (e.g. vandalism, poor schoolwork, attacks people) appeared to be relatively serious. In contrast, the 20 least referable problems (e.g. bragging, teases a lot, likes to be alone) appeared less so. Weiss (personal communication, March 4, 1992) indicated that, for boys, the CBCL item ‘wishes to be of opposite sex’ had an RI of 91/118 (in the upper quartile) and ‘behaves like opposite sex’ had an RI of 80/118. For girls, the RI was lower: 55/118 for ‘wishes to be of opposite sex’ and 14/118 for ‘behaves like opposite sex’. Weisz & Weiss’ (1991) study, together with studies from the normative literature, led us to predict that referred girls would display more extreme cross-gender behaviour than referred boys, which might account, at least in part, for the disparity by sex in referral rates. Zucker *et al.* (1997a) provided some data that supported this prediction, suggesting therefore that girls may need to display more cross-gender behaviour than boys before a referral is initiated. However, it is important to note that the sexes did not differ in the percentage who met the complete DSM criteria for GID; thus, there was no gross evidence for a sex difference in false-positive referrals.

Diagnosis and assessment

Diagnosis

DSM-IV diagnosis of gender identity disorder

In DSM-IV, there were some changes in the conceptualization of GID and in the diagnostic criteria; for example, there was a reduction of diagnostic categories from three to one between DSM-III-R (American Psychiatric Association 1987) and DSM-IV. The DSM-IV Subcommittee on Gender Identity Disorders (Bradley *et al.* 1991) took the position that the DSM-III-R diagnoses of gender identity disorder of childhood, transsexualism, and gender identity disorder of adolescence or adulthood, non-transsexual type were not qualitatively distinct disorders, but reflected differences in both developmental and severity parameters. As a result, the DSM-IV Subcommittee recommended one overarching diagnosis, gender identity disorder, that could be used, with appropriate variations in criteria, across the life cycle.

In DSM-IV, three criteria are required for the diagnosis, with one exclusion criterion. The first criterion (A) reflects the child's cross-gender identification, indexed by five behavioural characteristics, of which at least four must be present. The second criterion (B) reflects the child's rejection of his or her anatomic status and/or rejection of same-sex stereotypical activities and behaviours. The third criterion (D) specifies that the 'disturbance . . . causes clinically significant distress or impairment in social, occupational, or other important areas of functioning' (American Psychiatric Association 2000, p. 581). The exclusion criterion (C) pertains to the presence of a physical intersex condition (for discussion on this point see Meyer-Bahlburg 1994).

Reliability and validity

Can the DSM-IV diagnosis of GID be made reliably? Because the criteria have changed and because no field trials were conducted, this question cannot yet be answered; however, previous versions of the criteria have shown strong evidence for both reliability and validity (Zucker & Bradley 1995).

Distress and impairment

As noted by Zucker (1992), the DSM-III-R did not provide guidelines regarding the assessment of distress in the A criterion ('persistent and intense distress' about being a boy or a girl) or the ways in which it might be distinct from other operationalized components in the criteria (the 'desire' to be of the other sex). In the DSM-IV, this problem persists, except that it is now located in D, and there is the additional problem of defining impairment.

The inclusion of a distress/impairment criterion ('a clinical significance criterion'; American Psychiatric Association 2000, p. 8) is not unique to GID; in fact, this criterion now appears in most of the DSM-IV diagnoses. Very little empirical work pre-

ceded the introduction of the criterion (Spitzer & Wakefield 1999). Indeed, the DSM-IV states that assessment of distress and impairment 'is an inherently difficult clinical judgement' (American Psychiatric Association 2000, p. 8).

For children with GID, we need to ask two interrelated questions: are they distressed by their condition, and, if so, what is the source of the distress? Regarding these questions, there are two broad views. One view is that children with GID become distressed about their cross-gender behaviour only after it has been interfered with (Stoller 1975). Stoller argued that marked cross-gender identification (in boys) was ego-syntonic because the putative familial psychodynamics that produced it were systemically syntonic. The other view is that the distress is caused by psychopathology in the child and in the family. Coates & Person (1985) claimed that GID is a 'solution' to specific forms of psychopathology in the child, particularly separation anxiety and 'annihilation' anxiety, which were induced by familial psychopathology.

It is conceivable that both views are correct or that one or the other better fits individual cases. However, the latter view is more compatible with the notion of inherent distress, whereas the former is more compatible with the notion that social pathology creates individual pathology. Clinical experience suggests that many youngsters with GID feel a sense of discomfort regarding their status as boys or girls from a very early age, which matches nicely with the DSM notion of distress. Nevertheless, there are youngsters in whom the behavioural characteristics of GID appear to be ego-syntonic and who experience distress only when their cross-gender behaviour is interfered with. The exact manner in which we should measure the putative distress of children with GID has not been worked out (Zucker 1999a); this holds true not only for GID but also for all of the other childhood psychiatric conditions that include the distress/impairment criterion.

Regarding impairment, there are several domains that this might be manifest in children with GID. Such children seem to have more trouble than others with basic cognitive concepts concerning their gender. Zucker *et al.* (1993b) found that children with GID were more likely than controls to misclassify their own gender. Zucker *et al.* (1999b) provided additional evidence that children with GID appeared to have a 'developmental lag' in the acquisition of gender constancy. Given the ubiquity of gender as a social category, this may well lead to affective confusion in self-representation and in social interactions. There is also evidence that children with GID have poorer peer relations than controls and more general behavioural problems, possible indices of impairment (Zucker & Bradley 1995; Zucker *et al.* 1997a).

Assessment

Biomedical tests

There are no known biological markers that can identify children with GID. Gross parameters of biological sex, such as the

sex chromosomes and the appearance of the external genitalia, are invariably normal. Because gender identity conflict is overrepresented among specific physical intersex conditions, particularly congenital adrenal hyperplasia (CAH) in genetic females, partial androgen-insensitivity syndrome in genetic males reared as girls, and in genetic males with cloacal exstrophy reared as girls (for review see Meyer-Bahlburg 1994; Zucker 1999b), it is important to enquire about any physical signs of these conditions; however, it is rare that these conditions have not already been diagnosed prior to a clinical assessment for GID.

Psychological tests

A number of parent-report and behavioural measures can be used to assess sex-typed behaviour in children with GID (Zucker 1992; Zucker & Bradley 1995). No one test is a replacement for a diagnosis that is established by a clinical interview that covers the behavioural signs for GID. Nevertheless, these measures have strong discriminant validity and constitute one strong line of evidence that GID is, in fact, a distinct syndrome. As reviewed elsewhere, data from psychological tests show a consistent pattern in that the percentage of false-positives appears to be lower than the percentage of false-negatives (Zucker 1992; Zucker & Bradley 1995).

One useful clinical instrument is the Gender Identity Interview for Children, shown in Table 44.1. Based on factor analysis, Zucker *et al.* (1993b) identified two factors: Affective Gender Confusion (questions 6–12) and Cognitive Gender Confusion (questions 1–4). Cut-off scores of either three or four deviant responses yielded high specificity rates (88.8 and 93.9%, respectively), but lower sensitivity rates (54.1 and 65.8%, respectively).

Associated psychopathology

Comorbidity (the presence of two or more psychiatric disorders) occurs frequently among children referred for psychiatric evaluation. Assuming that the putative comorbid conditions actually represent distinct disorders, it is important to know, for various reasons (e.g. prevention and treatment planning), whether one condition increases the risk for the other condition or if the conditions are caused by distinct or overlapping factors (Caron & Rutter 1991).

Among children with GID, several measurement approaches have been employed to address this matter, including standardized behaviour problem questionnaires, ratings of social behaviour in structured situations and on questionnaires, assessment of personality functioning and structure on projective tests, assessment of quality of attachment with the mother, and ascertainment of other psychiatric disorders. Most of this work has focused on boys with GID, for which a detailed summary may be found elsewhere (Zucker & Bradley 1995).

The greatest amount of information on general behaviour

Table 44.1 Gender identity interview for children (boy version). (From Zucker *et al.* (1993b))

1	Are you a boy or a girl? BOY/GIRL
2	Are you a (opposite of first response)?
3	When you grow up, will you be a Mommy or a Daddy? MOMMY/DADDY
4	Could you ever grow up to be a (opposite of first response)? YES/NO
5	Are there any good things about being a boy? YES/NO If YES, say: Tell me some of the good things about being a boy (probe for a maximum of three responses)
6	Are there any things that you don't like about being a boy? YES/NO If YES, say: Tell me some of the things that you don't like about being a boy (probe for a maximum of three responses)
7	Do you think it is better to be a boy or a girl? YES/NO Why? (probe for a maximum of three responses)
8	In your mind, do you ever think that you would like to be a girl? YES/NO If YES, ask: Can you tell me why? (probe for a maximum of three responses)
9	In your mind, do you ever get mixed up and you're not sure if you are a boy or a girl? YES/NO If YES, say: Tell me more about that (probe until satisfied)
10	Do you ever feel more like a girl than like a boy? YES/NO If YES, say: Tell me more about that (probe until satisfied)
11	You know what dreams are, right? Well, when you dream at night, are you ever in the dream? If YES, ask: In your dreams, are you a boy, a girl, or sometimes a boy and sometimes a girl? BOY/GIRL/BOTH/NOT IN DREAMS (probe regarding content of dreams)
12	Do you ever think that you really are a girl? YES/NO If YES, say: Tell me more about that (probe until satisfied)

problems comes from parent-report data using the CBCL and the Teacher's Report Form (Achenbach & Edelbrock 1986). On these measures, clinic-referred boys and girls with GID show significantly more general behaviour problems than their siblings and non-referred ('normal') children. Given that the siblings and non-referred children do not engage, on average, in marked cross-gender role behaviour, this might be construed as evidence for a relation between cross-gender role behaviour and general behaviour problems. The situation is clearly more complicated than this because demographically matched clinical controls (who, on average, show typical gender role behaviour) show comparable levels of behaviour problems to the children with GID (Zucker & Bradley 1995).

On the CBCL, boys with GID have a predominance of emotional difficulties, whereas girls with GID do not (Zucker & Bradley 1995). Boys with GID have also been found to show high rates of separation anxiety traits (Coates & Person 1985; Zucker *et al.* 1996a; Birkenfeld-Adams 1999). At present, reasons for this associated psychopathology have been best studied

in boys with GID (Zucker & Bradley 1995). CBCL behaviour problems are positively associated with age, which may reflect the result of increasing social ostracism, particularly in the peer group. It is also associated with a composite index of maternal psychopathology, which may reflect generic, non-specific familial risk factors in producing behaviour problems in general. The predominance of emotional psychopathology may reflect familial risk for affective disorders and temperamental features of the boys. The extent to which aspects of the behavioural psychopathology may actually induce the emergence of the GID itself remains unresolved (see below).

Aetiological influences

Both biological and psychosocial factors have been proposed to account for the development of GID in children. In this section, I review some of the factors identified in the literature believed to be associated with an increased ‘risk’ for the development of GID.

Biological factors

Children with GID invariably do not show signs of a gross physical intersex condition, which would rule out a marked prenatal hormonal anomaly. Thus, the search for biological influences on the development of GID must focus on factors that are, perhaps, more subtle or at least on factors that do not affect the configuration of the external genitalia. In this regard, research strategies parallel those that have been used in the study of sexual orientation differentiation because, again, there is no evidence for the presence of gross hormonal abnormalities that would implicate the presence of a physical intersex condition (Meyer-Bahlburg 1984).

Activity level and rough-and-tumble play

Activity level (AL) is a commonly accepted dimension of temperament, with some evidence for a genetic basis (Willerman 1973; Saudino & Eaton 1991) and possibly prenatal hormonal influences (Ehrhardt & Baker 1974). Regarding children with GID, AL as a risk factor is a promising possibility, because it shows a rather strong sex difference, with boys having a higher AL than girls (Eaton & Enns 1986; Campbell & Eaton 1999). Rough-and-tumble (RT) play, another sex-dimorphic behaviour, bears some similarity to AL, in that it is often characterized by high energy expenditure; however, a distinguishing feature of RT is that it is a social interactive behaviour involving such sequences as ‘play fighting’ and ‘chasing’. Using parent-report measures of AL, two studies found that boys with GID had a lower AL than control boys (Bates *et al.* 1979; Zucker & Bradley 1995). Zucker & Bradley (1995) also found that girls with GID had a higher AL than control girls; indeed, the girls with GID had a higher AL than the boys with GID, whereas for the controls the typical sex difference was observed. It is possible there-

fore that a sex-atypical AL is a risk factor that predisposes to the development of GID. For example, a low-active boy with GID may find the typical play behaviour of other boys to be incompatible with his own behavioural style (Ruble & Martin 1998), which might make it difficult for him to integrate successfully into a male peer group.

Perhaps these within-sex variations in AL are related to subtle variations in patterns of prenatal hormonal secretion and converge with recent studies in the experimental animal literature. Among female rhesus monkey offspring, it has been possible, by varying the timing of exogenous administration of hormones during the pregnancy, to alter the normal patterning of sex-dimorphic behaviour but to keep normal genital differentiation intact (Goy *et al.* 1988). This animal model—which shows a *dissociation* between sex-dimorphic behavioural differentiation and genital differentiation—has the most direct relevance for explaining the marked cross-gender behaviour of children with GID.

Birth weight

On average, males weigh more than females at the time of birth (Arbuckle *et al.* 1993). There are, of course, many factors that influence variations in birth weight. One hypothesized factor is the sex difference in prenatal exposure to androgens. In one study, girls with CAH had a higher mean birth weight than unaffected girls (Qazi & Thompson 1971). In another study, genetic males with the complete form of the androgen insensitivity syndrome were comparable in birth weight to that of genetic females (de Zegher *et al.* 1998).

Zucker *et al.* (1999a) compared the birth weights of boys with GID and clinical control boys and girls. The clinical controls showed the expected sex difference in birth weight, with an effect size of 0.29 (Cohen’s *d*). The boys with GID had a significantly lower birth weight than the clinical control boys ($d = 0.18$), but did not differ significantly from the clinical control girls. Although it is not clear what factor or set of factors account for the proband-control difference in birth weight, the results are consistent with the possible role of prenatal hypoandrogenization among the GID probands.

Handedness

Slightly more males than females show a preference for using the left hand in unimanual behavioural tasks, such as writing. There is no established consensus for understanding the basis of this sex difference but genetic factors clearly have a role in determining hand preference. Another line of research implicates adverse prenatal and/or perinatal events that result in an elevation in left-handedness above the approximate gold standard of 10% in the general population.

Zucker *et al.* (2001) found that boys with GID ($n = 205$) had a significantly elevated rate of left-handedness (19.5%) when compared to three separate quasi-epidemiological samples of boys (11.8%, total $n = 14\,253$) and with a diagnostically hetero-

geneous sample of clinical control boys (8.3%, $n=205$). This finding parallels studies of adult males with GID, who also appear to have an elevated rate of left-handedness (Herman-Jeglinska *et al.* 1997), as well as studies of adult men with a homosexual sexual orientation (Lalumière *et al.* 2000). At present, the explanation for the elevation remains unclear, but candidate factors have centred on some type of perturbation in prenatal development that, in some way, affects sex-dimorphic behavioural differentiation.

Sibling sex ratio and birth order

Boys with GID have an excess of brothers:sisters (sibling sex ratio) and have a later birth order (Blanchard *et al.* 1995; Zucker *et al.* 1997b). Some additional evidence shows that boys with GID are born later, primarily in relation to the number of older brothers but not sisters. In the Blanchard *et al.* study, clinical control boys showed no evidence for an altered sibling sex ratio or a late birth order. One biological explanation to account for these results pertains to maternal immune reactions during pregnancy. The male fetus is experienced by the mother as more 'foreign' (antigenic) than the female fetus. Based on studies with lower animals, it has been suggested that one consequence of this is that the mother produces antibodies that have the effect of demasculinizing or feminizing the male fetus, but no corresponding masculinizing or defeminizing of the female fetus (Blanchard & Klassen 1997). This model would predict that males born later in a sib-line might be more affected, because the mother's antigenicity increases with each successive male pregnancy, which is consistent with the empirical evidence on sibling sex ratio and birth order among GID probands. At present, however, this proposed mechanism has not been formally tested in humans.

Summary

In summary, research over the past decade has begun to identify some characteristics of children with GID, particularly in boys, that may well have a biological basis. Corresponding studies of girls have been fewer in number, largely because of problems in sample size that limit statistical power. In many respects, it has been easier to rule out candidate biological explanations, such as the influence of gross anomalies in prenatal hormonal exposure, than it has been to identify the relevant biological mechanisms that are involved in affecting sex-dimorphic behavioural differentiation but not sex-dimorphic genital differentiation. However, the identification of new potential biological markers may open up avenues for further empirical inquiry.

Psychosocial factors

Psychosocial factors, to truly merit causal status, must be shown to influence the emergence of marked cross-gender behaviour in the first few years of life. Otherwise, such factors would be better conceptualized as perpetuating rather than predisposing.

Sex assignment at birth

Because most children with GID do not have a co-occurring physical intersex condition, sex assignment at birth is invariably in accordance with the external markers of biological sex. In some physical intersex conditions, sex assignment is delayed and, on occasion, changed from the initial sex assignment. It has been argued that prolonged delay or uncertainty about the child's 'true' sex can contribute to gender identity conflict in affected individuals (Money *et al.* 1957; Meyer-Bahlburg *et al.* 1996). This does not, however, appear to be the situation for children with GID.

Parents' sexual orientation

There is little evidence to suggest that the sexual orientation of parents is related to GID in children. Studies of lesbian mothers and gay fathers have not, to date, indicated an overrepresentation of GID among their offspring. In fact, the children of gay and lesbian parents appear to have fairly typical gender identity and gender role development when compared to the children of heterosexual parents (Golombok *et al.* 1983; Green *et al.* 1986; Tasker & Golombok 1997). In our own clinic, we have not detected any convincing evidence for an elevation in the rate of a homosexual sexual orientation among the parents of both children and adolescents with GID.

Prenatal gender preference

It is common for parents to express a prenatal gender preference. Other things being equal, parents will have a child of the non-preferred sex about 50% of the time. Are parents of children with GID more likely than control parents to report having had a desire for a child of the opposite sex? The simple answer appears to be no, at least with regard to the mothers of boys with GID (Zucker *et al.* 1994). We did find, however, that the maternal wish for a girl was significantly associated with the sex composition and birth order of the sibship. Among the GID boys with only older brothers, the percentage of mothers who recalled a desire for a daughter was significantly higher than among the probands with other sibship combinations; however, the same pattern was observed in a control group (Zucker *et al.* 1994).

Social reinforcement of cross-gender behaviour

Understanding the role of parent socialization in the genesis and/or perpetuation of GID (e.g. via reinforcement principles or modelling) has been influenced by the normative developmental literature on sex-dimorphic sex-typed behaviour (Ruble & Martin 1998). It has also been influenced by the seminal observations of Money *et al.* (1957) that the rearing environment was the predominant determinant of gender identity in children with physical intersex conditions.

It should be recognized that some critics are quite sceptical of

the role of parent socialization in inducing sex differences in sex-typed behaviour among ordinary children (Lytton & Romney 1991) or within-sex variations. In recent years, the importance of the rearing environment has also been questioned within the literature on physical intersex conditions (for review see Zucker 1999b). This literature has recently been discussed in relation to the long-term gender identity outcome of a normal boy whose penis was accidentally ablated during a routine circumcision at 7 months, and who was subsequently reassigned as a girl around the age of 2 years. A female gender identity was judged to have differentiated and was maintained to at least age 9 years (Money 1975). Longer term follow-up, however, revealed that the patient reverted to living as a male in early adolescence (Diamond & Sigmundson 1997), which has been interpreted by some to indicate a much stronger role for biological rather than psychosocial influences on gender identity differentiation. However, critics have pointed out that there are alternative interpretations to this case (Meyer-Bahlburg 1999a). Moreover, in another case of ablatio penis, in which a gender reassignment to female occurred at 7 months, the patient's gender identity was judged to be unequivocally female at age 26 (Bradley *et al.* 1998). It is against this backdrop of competing views on the role of socialization that the literature on GID must be appraised.

Clinicians of diverse theoretical persuasions have consistently reported that the parental response to early cross-gender behaviour in children with GID is typically neutral (tolerance) or even encouraging (for review see Zucker & Bradley 1995). Regarding boys with GID, Green (1974) assessed parental recall of such responses taken from clinical and structured interviews at the time of assessment and concluded that 'what comes closest so far to being a *necessary* variable is that, as any feminine behaviour begins to emerge, there is *no* discouragement of that behaviour by the child's principal caretaker' (p. 238, italics in original; see also Green 1987; Roberts *et al.* 1987). In our clinic, Mitchell (1991), in a structured interview study, found that mothers of GID boys were more likely to tolerate/encourage feminine behaviours and less likely to encourage masculine behaviours than were the mothers of both clinical and normal control boys. The following vignette of parents of a 4-year-old boy is illustrative.

Interviewer (I): What is the first memory that you have of Eric's interest in 'girls' things?

Mother (M): Well, when he was about 2, he started to wear my shoes. He would wear them every day.

I: What did you think about that?

M: I thought it was cute, the way he was clumping around in them.

I: What about you (to father)?

Father (F): I wasn't around much, working and all, so I didn't see much of it. She (his wife) told me about it and I said that I didn't like it, but what can you do?

I: What happened after that?

M: Well, then he got interested in my dresses (laughs) and he looked so cute, running around in the heels and my long dress. We even took pictures of him like that.

F: Yeah, right.

I: Anything else?

M: When I took him to the toddler group, he went immediately over to the girls and he got into the Barbie dolls. He seemed obsessed with their hair and we wound up buying him 3 or 4 of them. His favourite one is the Barbie with roller-blades. I asked his doctor about it when he was 3 and the doctor said that it was a phase and that he would grow out of it.

F: Yeah, and then he was pretending that he was a girl all the time and said that he would grow up and be a mommy, and then he said that he wanted to cut off his penis.

I: What happened when he said that?

M: Well, that's why we're here. I'm getting worried that he won't grow out of it...it's getting worse.

I: Before he said that he wanted to cut off his penis, how do you think you have reacted to his interest in the girls' things over the past couple of years?

M: Well, I've pretty well let him do what he wants and, anyways, the doctor told me not to worry. I thought that if he played with the Barbies, maybe he'd be a good father, but he doesn't want to be the father, he's only pretending to be me.

F: Yeah, I'm getting more worried myself, but my wife told me not to be so worried and, well, you know, she's kind of the boss when it comes to raising the kids.

Of course, the limitations of this kind of interview data need to be recognized. None the less, one aspect of these data deserves special comment. Clinicians of diverse theoretical persuasions have observed the apparent tolerance, or even encouragement, of feminine behaviour shown by parents of boys with GID. However, the fact that these parents have sought out a clinical assessment usually means that they are now concerned about their child's gender identity development (Zucker 2000a). From the standpoint of attribution theory (Weiner 1993), one might predict that parents would minimize their encouragement or tolerance of cross-gender behaviour, as it has such an obvious bearing on 'causality'. Yet a majority of the parents whom we have assessed do not recall systematic efforts to limit or redirect their child's cross-gender behaviour, particularly during the initial period of symptom onset and for various periods of time thereafter.

The reasons why parents might tolerate, if not encourage, early cross-gender behaviours appear to be quite diverse, suggesting that the antecedents to this 'end state' are multiple in origin. Some parents report being influenced by ideas regarding non-sexist child-rearing. In other parents, the antecedents seem to be rooted in pervasive conflict that revolves around gender issues. For example, a small subgroup of mothers (about 10%) of boys with GID appear to experience something akin to what we have termed *pathological gender mourning* (Zucker 1996). During the pregnancy, there is a strong desire for a girl; in all of the cases, the mother had already borne at least one other son, but no daughter — except in three instances in which the daughter was given up for adoption (one case) or had died in infancy (two cases). After the birth of the 'non-preferred' son, this wish seems to colour strongly the mother's perception and relation-

ship with her newborn, and there are strong signs of ambivalence about his gender status. Zucker (1996) identified at least 10 possible signs of pathological gender mourning, including severe post-partum depression related to the birth of a son, recurrent nightmares about being pregnant with a girl, delayed naming, and active cross-dressing of the boy (for further details see Zucker *et al.* 1993a; Zucker & Bradley 1995, 2000). In our clinical experience, the most common psychological trait associated with the strong wish for a daughter is the need to nurture and be nurtured by a female child, which often reflects compensatory needs originating in childhood (Gibson 1998).

Maternal emotional functioning

The role of maternal psychopathology in the genesis and perpetuation of GID has received a great deal of clinical and theoretical attention but, unfortunately, only limited empirical evaluation. At the outset, it should be noted that the available empirical studies have been delimited to the mothers of boys with GID—comparable studies are not available regarding the mothers of girls with GID (for descriptive data see Zucker & Bradley 1995, pp. 252–253).

Marantz & Coates (1991) found that the mothers of boys with GID showed more signs of psychopathology than did the mothers of demographically matched normal boys, including more pathological ratings on the Diagnostic Interview for Borderlines and more symptoms of depression on the Beck Depression Inventory.

Over the past several years, our group has collected systematic data on maternal psychopathology and marital discord, some of which was reported by Mitchell (1991) and Zucker & Bradley (1995). To date, our data show that, on average, mothers of boys with GID have levels of emotional distress and psychiatric impairment comparable to that of clinical control mothers, but higher than that of normal control mothers. We did not, however, detect between-group differences on a measure of marital discord.

On one measure—the Symptom Checklist 90–Revised—mothers of GID boys had higher scores on most of the subscales and the composites than did the mothers of the normal control boys, whereas the scores of the clinical control mothers fell in between the two other groups. The GID mothers had peak scores on the Obsessive-Compulsive, Depression, and Hostility subscales. On another measure, the Diagnostic Interview Schedule (DIS), 30% of the mothers (total $n=140$) had two DIS diagnoses and 24% had three or more DIS diagnoses. The most common diagnoses were major depressive episode (39.6%) and recurrent major depression (32.1%). Overall, the rate of psychiatric impairment appears to be higher than our available data on mothers of both the clinical control and normal boys. Because more control group mother data are required, these results should be viewed cautiously. None the less, it is apparent by reference to epidemiological data that, on average, mothers of GID boys have a history of psychiatric disorder that is elevated.

The emerging data on emotional distress and psychiatric im-

pairment in the mothers of boys with GID indicate that it is more common than in the mothers of normal control boys and at least comparable to the mothers of clinical control boys. Still, we are left with the problem of specificity (Garber & Hollon 1991), in that these maternal characteristics are not unique to the mothers of GID boys, but common to the mothers of clinic-referred boys in general. Accordingly, maternal emotional distress/impairment functions, at best, only as a non-specific risk factor in the development of GID. If the mother's emotional state truly is involved in the genesis of GID, then there should be evidence of psychiatric impairment prior to and during the emergence of the child's symptoms. The data are suggestive that this is the case, and that the presence of emotional difficulties in the mothers is not simply a reaction to having a child with GID (Zucker & Bradley 1995, p. 123).

Coates has argued that the presence of psychopathology renders the mothers emotionally unavailable, which results in anxiety and insecurity in the son, and that it is this state of affairs that is partly responsible for symptom onset. Indeed, Coates & Person (1985) advanced a very specific hypothesis; that the erratic and uneven emotional availability of the mothers activated separation anxiety in the boys, which, in turn, activated the symptoms of GID: 'In imitating "Mommy" [the boy] confuse[s] "being Mommy" with "having Mommy"'. [Cross-gender behaviour] appears to allay, in part, the anxiety generated by the loss of the mother' (p. 708). Indeed, boys with GID appear to have high rates of separation anxiety traits, as judged by maternal report on a structured interview schedule (Zucker *et al.* 1996a) and their own responses on the Separation Anxiety Test (Birkenfeld-Adams 1999).

The possible role of separation anxiety in the genesis of GID raises more general questions about the quality of the mother-son relationship. Over the past few years, our group has examined the quality of attachment to the mother among young boys and girls with GID (ages 3–6 years). Among a sample of 22 boys, Birkenfeld-Adams (1999) found that the majority (73%) were classified as insecurely attached, a rate comparable to that of an internal clinical control group and of other studies of clinical populations (Greenberg *et al.* 1991).

Because insecure attachments and separation anxiety are likely to be non-specific risk factors (many boys who have these qualities do not have GID), the crucial question that remains is why only a small minority of boys develop the 'fantasy solution' of wanting to be a girl. Various predisposing factors have been implicated, including temperamental characteristics of the child, the premorbid relationship with the mother, the position of the father in the family system, that the family psychopathology must occur during the putative sensitive period for gender identity formation (Money *et al.* 1957), and so on. However, at present the question of specificity remains unanswered in any satisfactory manner.

One possible mediating variable might be the importance of the child's gender to the mother or her attitudes towards men and masculinity in general. In this regard, pathological gender mourning, as discussed earlier, may be a potential prototype.

Pathological gender mourning appears to be part of the family history in only a small minority of cases and thus other pathways are required to account for the role of maternal impairment in the genesis of GID.

It appears therefore that there are diverse pathways that lead to how parents respond to the child's early cross-gender behaviour, either by encouraging or tolerating it. Thus, from a clinical and therapeutic point of view, it is important to identify the putative motivations with regard to the selective reinforcement of sex-typed behaviours.

Paternal emotional functioning

The role of paternal influences in the genesis and perpetuation of GID has also received a great deal of clinical and theoretical attention but, again, only limited empirical evaluation, which has been delimited to the fathers of boys with GID.

One account implicates the father's role by virtue of his absence from the family matrix. Across 10 samples of boys with GID, the rate of father absence (e.g. because of separation or divorce) was 34.5% (summarized in Zucker & Bradley 1995). It is unlikely, however, that this rate would differ significantly from the rate found in clinical populations in general, if not the general population. Green (1987) found that paternal separations occurred earlier in the families of GID boys than in normal control boys, so it is possible that timing is an additional variable to consider. Green (1987) also found that the fathers of GID boys (both father-present and father-absent) recalled spending less time with their sons than did the fathers of control boys during the second year of life, years 3–5, and at the time of assessment. The inclusion of a clinical control group would be helpful in gauging the specificity of this finding.

Unfortunately, there is little in the way of systematic research on paternal psychopathology. Wolfe (1990) conducted a small but detailed study of 12 fathers, predominantly of an upper middle-class background, of boys with GID. On the Structured Clinical Interview for DSM-III, all of the fathers received an Axis I diagnosis for either a current or past disorder (most frequently substance abuse and depression) and eight also received at least one Axis II diagnosis. Unpublished DIS data from our own clinic on 90 fathers indicate that alcohol abuse (22.2%) has been the most common diagnosis. This percentage may underestimate the prevalence of alcohol abuse in fathers of GID boys, because we were not able to interview a substantial number of fathers who were no longer part of the family matrix. On the other hand, it should be noted that about half the fathers who were interviewed did not meet criteria for any DIS diagnosis. Whatever the exact patterning of paternal emotional functioning proves to be, the same issues of interpretation discussed earlier regarding mothers apply.

Summary

In summary, data on psychosocial influences have been able to rule out some hypothesized pathways and have lent some sup-

port for others. Social reinforcement of cross-gender behaviour when it first appears in the toddler and preschool years appears to be the most common psychosocial influence on the disorder's consolidation. The role of family influences, including parental psychiatric impairment and emotional distress, appears to be an important area for further empirical inquiry.

Long-term follow-up

Green (1987) has conducted the most extensive long-term follow-up of feminine boys, the majority of whom would likely have met DSM criteria for GID. This study can be used as a benchmark for the other published follow-up reports, which have been summarized in detail elsewhere (Zucker 1985, 1990). At the moment, insufficient numbers of girls with GID have been followed prospectively to draw conclusions about long-term outcome. Green's (1987) study contained 66 feminine and 56 control boys assessed initially at a mean age of 7.1 years (range, 4–12). Forty-four feminine boys and 30 control boys were available for follow-up at a mean age of 18.9 years (range, 14–24). The majority of the boys were not in therapy between assessment and follow-up.

Sexual orientation in fantasy and behaviour was assessed by means of a semistructured clinical interview. Kinsey ratings were made on a 7-point continuum, ranging from exclusive heterosexuality to exclusive homosexuality (Kinsey *et al.* 1948). Depending on the measure (fantasy or behaviour), 75–80% of the previously feminine boys were either bisexual or homosexual at follow-up vs. 0–4% of the control boys. Green also reported on the gender identity status of the 44 previously feminine boys. He found that one youngster, at the age of 18 years, was gender-dysphoric to the extent of considering sex-reassignment surgery.

In a more recent study, Cohen-Kettenis (2001) reported a persistence of gender dysphoria into adolescence that appears to be considerably higher than that reported on by Green (1987). Of 129 children referred between 4–12 years, 74 had now reached adolescence. Of these, Cohen-Kettenis reported that 17 (23%) had applied for sex-reassignment. Their mean age at assessment had been at 9 years (range, 6–12), which was a couple of years older than the mean age at assessment in Green's study. About half were reported to be living full-time in the cross-gender role, six were taking puberty-blocking medication and three were taking cross-sex hormones; however, none had of yet gone through any surgical procedure. From the Cohen-Kettenis report, it is not clear if any of these youngsters had had treatment for their GID during childhood.

The prospective data are consistent with retrospective studies of adults with a homosexual sexual orientation, which have repeatedly shown that homosexual men and women recall more cross-gender behaviour in childhood than heterosexual men and women (Bailey & Zucker 1995). Thus, there is now sufficient evidence, from both retrospective and prospective studies, to conclude that childhood sex-typed behaviour is strongly as-

sociated with later sexual orientation, which represents one of the more powerful illustrations of developmental continuity to emerge from research in developmental psychiatry. Recall interviews with both adolescents and adults with GID (with a homosexual sexual orientation) almost invariably document a childhood cross-gender history. The prospective studies of children, however, show that the disorder persists into adolescence or adulthood for only a small minority. Thus, there is a marked disjunction between the prospective and retrospective studies.

How might this disjunction be explained? In some respects, the situation is comparable to that which has been found for other child psychiatric disorders. Adults with antisocial personality disorder invariably will have had a childhood history of oppositional defiant disorder and conduct disorder. Yet, the vast majority of children with oppositional defiant disorder and the majority of children with conduct disorder followed prospectively will not be diagnosed with antisocial personality disorder in adulthood (Zoccolillo *et al.* 1992; Lahey *et al.* 2000).

Regarding children with GID, then, we need to understand why, for the majority, the disorder apparently remits by adolescence, if not earlier. One possible explanation concerns referral bias. Green (1974) argued that children with GID who are referred for clinical assessment (and then therapy) may come from families in which there is more concern than is the case for adolescents and adults, the majority of whom did not receive a clinical evaluation and treatment during childhood. Thus, a clinical evaluation and subsequent therapeutic intervention during childhood may alter the natural history of GID. This is only one account of the disjunction and there may well be additional factors that might distinguish those children who are more strongly at risk for the continuation of the disorder from those who are not. Another explanation is that the diagnostic criteria for GID, at least as they are currently formulated, simply are not sharp enough to distinguish children who are more likely to show a persistence in the disorder from those who are not.

To date, very little has been done in the way of assessing the more general psychosocial and psychiatric outcomes of children with GID. This is important for at least two reasons. First, children with GID show, on average, as much general behavioural psychopathology as do demographically matched clinical controls. Whether children with GID will continue to be at risk for more general disturbances in psychiatric functioning as they mature remains an understudied area of empirical inquiry. In a recent cross-sectional study, Zucker *et al.* (2001) compared children and adolescents with GID and found that the adolescents were substantially more disturbed on the CBCL than were the children, even after co-varying for various differences in demographic characteristics. Secondly, we now know that gay and lesbian adolescents, without known GID in childhood, are at increased risk for mental health problems although the reasons for this have been largely understudied (Remafedi *et al.* 1998; Fergusson *et al.* 1999; Garofalo *et al.* 1999a,b). Presumably, some of the variance is related to the stigma of a minority sexual orientation (Meyer 1995). It could be argued, for example, that

the severe social ostracism experienced by children with GID for their marked cross-gender behaviour increases the risk for general psychiatric problems (e.g. depression, suicidality), but this requires empirical verification.

Linkage between childhood sex-typed behaviour and sexual orientation

Because the linkage between GID in childhood and a later homosexual sexual orientation is so strong, understanding the connection is important, from both a theoretical and a clinical perspective. The most prominent biological explanation is that both sex-typed behaviour in childhood and sexual orientation in adolescence/adulthood are joined by some common factor or set of factors; for example, regarding genetic females with CAH, excessive prenatal exposure to androgens has been posited as the linkage factor that explains the higher rates of both behavioural masculinity during childhood (Berenbaum & Hines 1992) and bisexuality/homosexuality in adulthood (Zucker *et al.* 1996b).

Psychosocial perspectives have been varied. Green (1987) conjectured that, compared to control boys, a feminine boy's lack of close relationships with other boys and with his father might result in 'male affect starvation'. Thus, in adolescence and adulthood, homoerotic contact is used in some compensatory manner to achieve closeness with other males. This scenario is an example of accounting for a within-sex difference in a behavioural outcome (in this instance, sexual orientation); it is not clear if 'male affect starvation' during childhood would also account for a girl's later sexual attraction to males.

In Bem's (1996) developmental theory of sexual orientation, it is proposed that similar mechanisms are operative in the sexual object choice of feminine boys and feminine girls (and masculine boys and masculine girls). Bem's account is not so much a 'deficit' model, as is implied by the term 'affect starvation', but a 'difference' model. Bem proposed that variations in childhood 'temperaments' influence a child's preference for sex-typical or sex-atypical activities and peers:

These preferences lead children to feel different from opposite-sex or same-sex peers—to perceive them as dissimilar, unfamiliar, and exotic. This, in turn, produces heightened non-specific autonomic arousal that subsequently gets eroticized to that same class of dissimilar peers (Bem 1996, p. 320).

For feminine boys and feminine girls, males are 'exotic', whereas for masculine boys and masculine girls, females are 'exotic'. Bem's (1996) theory of sexual orientation represents a prototype in trying to unite typical and atypical development. However, there are many unanswered questions and alternative interpretations raised by the theory. Bem places great emphasis on temperamental factors that affect a child's preference for sex-typical or sex-atypical activities and friendships—an emphasis that might be disputed by some developmentalists (Ruble & Martin 1998). Empirical evidence for the emergence of specific erotic feelings following 'heightened non-specific autonomic

arousal' is scant, although it is quite likely that the relevant tests can be obtained through an analysis of emerging sexual interactions within the pre-adolescent peer group.

Bem's theory is intriguing in that it implies a greater potential for malleability in sexual orientation development than is apparent in some of the biological theories. If a feminine boy becomes more masculine in the course of his childhood, does this imply that the likelihood of later homoeroticism decreases? Conversely, if a feminine girl becomes more masculine in the course of her childhood, does this imply that the likelihood of later homoeroticism increases? Unfortunately, there is not much information available to answer these questions.

Green (1987) compared feminine boys who were subsequently classified as bisexual or homosexual with feminine boys who were subsequently classified as heterosexual. Although some feminine behaviours in childhood distinguished the two subgroups, a composite extent of femininity score only approached conventional levels of significance and only for the rating of sexual orientation in fantasy, not behaviour. The lack of a stronger correlation is somewhat surprising, because one might have expected an association between the degree of cross-gender identification and long-term outcome; however, Green (1987) did find that the continuation of certain feminine behaviours throughout childhood was associated with later homosexuality. Thus, it may be that the persistence of these feminine behaviours is more important than their extent during the early childhood years.

Treatment

In this section, I review some of the extant perspectives on treatment issues and what is known about the efficacy of various therapeutic interventions.

Ethical considerations

Any contemporary child clinician responsible for the therapeutic care of children and adolescents with GID will quickly be introduced to complex social and ethical issues pertaining to the politics of sex and gender in post-modern Western culture and have to think them through carefully. Is GID really a disorder or just a 'normal' variant of gendered behaviour? Is marked cross-gender behaviour inherently harmful or is it simply harmful because of social factors? If a teenager requests immediate cross-sex hormonal and surgical intervention as a therapeutic for gender dysphoria, should the clinician comply? If parents request treatment for their child with GID to divert the probability of a later homosexual sexual orientation, what is the appropriate clinical response? All of these questions force the clinician to think long and hard about theoretical and treatment issues.

Perhaps the most acute ethical issue concerns the relation between GID and a later homosexual sexual orientation. As noted earlier, follow-up studies of boys with GID, largely untreated, indicate that homosexuality is the most common long-term psy-

chosexual outcome. Some parents of children with GID request treatment, partly with an eye towards preventing subsequent homosexuality in their child, whether this is because of personal values, concerns about stigmatization, or for other reasons.

In the 1990s, this 'rationale' for treatment was subject to intense scrutiny (Sedgwick 1991; Minter 1999). Some critics have argued that clinicians, consciously or unconsciously, accept the prevention of homosexuality as a legitimate therapeutic goal (Pleak 1999). Minter (1999) has claimed, as have others (Scholinski 1997), that some adolescents in the USA are being hospitalized against their will because of their homosexual sexual orientation but under the guise of the GID diagnosis. These allegations have not been verified in any systematic manner and I know of no such case in which this has occurred (Meyer Bahlburg 1999b). Others have asserted, albeit without direct empirical documentation, that treatment of GID results in harm to children who are 'homosexual' or 'prehomosexual' (Isay 1997). Some clinicians have raised questions about differential diagnosis, arguing that there is not always an adequate distinction between children who are 'truly' GID vs. those who are merely prehomosexual (Corbett 1996; Richardson 1996, 1999).

The various issues regarding the relation between GID and homosexuality are complex—both clinically and ethically. Three points, albeit brief, can be made. First, until it has been shown that any form of treatment for GID during childhood affects later sexual orientation, the issue is moot. From an ethical standpoint, however, the clinician has an obligation to inform parents about the state of the empirical database. Secondly, I have argued elsewhere that some critics incorrectly conflate gender identity and sexual orientation, regarding them as isomorphic phenomena (Zucker 1999c), as do some parents. Psychoeducational work with parents can review the various explanatory models regarding the statistical linkage between gender identity and sexual orientation (Bailey & Zucker 1995; Bem 1996), but also discuss their distinctness as psychological constructs. Thirdly, many contemporary clinicians emphasize that the primary goal of treatment of children with GID is to resolve the conflicts that are associated with the disorder *per se*, regardless of the child's eventual sexual orientation. Most clinicians who have worked with children and adolescents with GID believe that they experience a great deal of suffering: many such youngsters are preoccupied with gender identity issues, they experience increased social ostracism and alienation as they get older, and show evidence of other behavioural and psychiatric difficulties. Most clinicians therefore take the position that therapeutics designed to reduce the gender dysphoria, lessen the degree of social ostracism, and to reduce the degree of psychiatric comorbidity constitute legitimate goals of intervention. How, then, might one go about reaching these therapeutic goals?

Developmental considerations

One aspect of the clinical literature suggests that there are important developmental considerations to bear in mind. For example, there is some evidence to suggest that GID is less re-

sponsive to psychosocial interventions during adolescence, and certainly by young adulthood, than it is during childhood. Thus, the lessening of malleability and plasticity over time in gender identity differentiation is an important clinical consideration.

Treatment of children

For children with GID, clinical experience suggests that psychosocial treatments can be relatively effective in reducing the gender dysphoria. Therapeutic approaches have included the most commonly used interventions for children in general, including behaviour therapy, psychodynamic therapy, parent counselling, and group therapy (for detailed reviews see Zucker 1985, 1990, 2001). In considering these various therapeutic approaches, there is one important sobering fact to contemplate: apart from a series of intrasubject behaviour therapy case reports from the 1970s, one will find not a single randomized controlled treatment trial in the literature (Zucker, 2001). Thus, the treating clinician must rely largely on the 'clinical wisdom' that has accumulated in the case report literature and the conceptual underpinnings that inform the various approaches to intervention.

Treatment for children with GID often proceeds on two fronts:

- 1 individual therapy with the child, in which efforts are made to understand the factors that seem to fuel the fantasy of wanting to become a member of the opposite sex and then to resolve them; and
- 2 parent counselling, in which efforts are made to help the child, in the naturalistic environment, to feel more comfortable about being a boy or a girl.

Treatment can address several issues. For youngsters who are quite confused about their gender identity, one can focus on the mastery of basic cognitive concepts of gender, including correct identification of the self as a boy or a girl; encouragement in the development of same-sex friendships, in which areas of mutual interest can be identified; and exploration of factors within the family that might be contributing to the gender identity conflict.

With parents, treatment issues include the following:

- 1 limit-setting of cross-gender behaviour and encouragement of gender-neutral or sex-typical activities;
- 2 factors within the family matrix that may be contributing to the child's gender identity conflict; and
- 3 parent factors, including psychiatric impairment, that may be compromising functioning in the parental role in general.

Here, I will focus on some technical aspects of limit-setting that are often misunderstood in the clinical literature and which thus require further explication. A common error committed by some clinicians is to simply recommend to parents that they impose limits on their child's cross-gender behaviour without attention to context. This kind of authoritarian approach is likely to fail, just as it will with regard to any behaviour, as it does not take into account systemic factors, both in the parents and in the child, that fuel the 'symptom'. At the very least, a psychoeducational approach is required, but, in many cases, limit-setting

needs to occur within the context of a more global treatment plan.

From a psychoeducational point of view, one rationale for limit-setting is that if parents allow their child to continue to engage in cross-gender behaviour, the GID is, in effect, being tolerated, if not reinforced. Thus, such an approach would contribute to the perpetuation of the condition. Another rationale for limit-setting is that it is, in effect, an effort to alter the GID from the 'outside in', while individual therapy for the child can explore the factors that have contributed to the GID from the 'inside out'. At the same time that one attempts to set limits, parents also need to help their child with alternative activities that might help consolidate a more comfortable same-gender identification. Encouragement of same-sex peer group relations can be an important part of such alternatives; for example, some boys with GID develop an avoidance of male playmates because they are anxious about rough-and-tumble play and fantasy aggression. Such anxiety may be fuelled by parent factors (e.g. where mothers conflate real aggression with fantasy aggression), but may also be fuelled by temperamental characteristics of the child (Zucker 2000b). Efforts on the part of parents to be more sensitive to their child's temperamental characteristics may be quite helpful in planning peer group encounters that are not experienced by the child as threatening and overwhelming. It is not unusual to encounter boys with GID who have a genuine longing to interact with other boys, but because of their shy and avoidant temperament do not know how to integrate themselves with other boys, particularly if they experience the contextual situation as threatening. Over time, with the appropriate therapeutic support, such boys are able to develop same-sex peer group relationships and begin to identify more with other boys as a result.

Another important contextual aspect of limit-setting is to explore with parents their initial encouragement or tolerance of the cross-gender behaviour. Some parents will tolerate the behaviour initially because they have been told, or believe themselves, that the behaviour is 'only a phase' that their child will grow out of. Such parents become concerned about their child once they begin to recognize that the behaviour is not merely a phase (Zucker 2000a). For other parents, the tolerance or encouragement of cross-gender behaviour can be linked to some of the systemic and dynamic factors described earlier. In these more complex clinical situations, one must attend to the underlying issues and work them through. Otherwise, it is quite likely that parents will not be comfortable in shifting their position.

Although many contemporary clinicians have stressed the important role of working with the parents of children with GID, one can ask if there is any empirical evidence that this is effective. Again, systematic information on the question is scanty. The most relevant study (Zucker *et al.* 1985) found some evidence that parental involvement in therapy was significantly correlated with a greater degree of behavioural change in the child at 1-year follow-up, but this study did not make random assignment to different treatment protocols, so one has to interpret the findings with caution.

Treatment of adolescents

If GID in adolescence is not responsive to psychosocial treatment, should the clinician recommend the same kinds of physical interventions that are used with adults (Harry Benjamin International Gender Dysphoria Association 1998)? Prior to such a recommendation, many clinicians usually encourage adolescents with GID to consider alternatives to this invasive and expensive treatment. One area of inquiry can therefore explore the meaning behind the adolescent's desire for sex reassignment and if there are viable alternative lifestyle adaptations. In this regard, the most common area of exploration pertains to the patient's sexual orientation. Almost all adolescents with GID recall that they always felt uncomfortable growing up as boys or as girls, but that the idea of 'sex change' did not occur until they became aware of homoerotic attractions. For some of these youngsters, the idea that they might be gay or homosexual is abhorrent. For some such adolescents, psychoeducational work can explore their attitudes and feelings about homosexuality. Group therapy, in which such youngsters have the opportunity to meet gay adolescents, can be a useful adjunct in such cases. In some cases, the gender dysphoria will resolve and a homosexual adaptation ensues (Zucker & Bradley 1995). For others, however, a homosexual adaptation is not possible and the gender dysphoria does not abate.

For adolescents in which the gender dysphoria appears chronic, the clinician can consider two main options:

- 1 management until the adolescent turns 18 and can be referred to an adult gender identity clinic; or
- 2 'early' institution of contra-sex hormonal treatment.

Regarding the latter, Gooren & Delemarre-van de Waal (1996) recommended that one option with gender-dysphoric adolescents is to prescribe puberty-blocking luteinizing hormone-releasing agonists (e.g. depot leuprolide or depot triptorelin) that facilitate more successful passing as the opposite sex. Thus, in male adolescents, such medication can suppress the development of secondary sex characteristics, such as facial hair growth and voice deepening, which makes it more difficult to pass in the female social role. Cohen-Kettenis & van Goozen (1997, 1998) reported that early cross-sex hormone treatment for adolescents under the age of 18 years, judged free of gross psychiatric comorbidity, facilitates the complex psychosexual and psychosocial transition to living as a member of the opposite sex and results in a lessening of the gender dysphoria.

Although such early hormonal treatment is controversial (Cohen-Kettenis 1994, 1995; Meyenburg 1994), it may well be the treatment of choice once the clinician is confident that other options have been exhausted. One issue that is not yet resolved concerns who are the best candidates for early hormonal treatments. Cohen-Kettenis & van Goozen (1997) have suggested that the least risky subgroup of adolescents with GID are those who show little evidence of psychiatric impairment. In my own clinic, the vast majority of adolescents with GID would not qualify on this basis (Zucker *et al.* in press). However, by adolescence, the issue is a tricky one because it is not clear to

what extent the psychiatric impairment is a consequence of the chronic gender dysphoria (Newman 1970). A randomized controlled trial would be useful in resolving the matter.

Future directions

In this chapter, I have provided an overview of the literature on GID in children and adolescents. Since GID first appeared in the DSM-III in 1980, considerable advances have been made in some areas. The phenomenology of GID is now well described and extant assessment procedures are available to conduct a thorough and competent diagnostic evaluation. Like other psychiatric disorders of childhood, it is apparent that complexity, not simplicity, is the guiding rule-of-thumb in any effort to make sense of the origins of GID. It appears that both biological and psychosocial factors contribute to the disorder's genesis and we are making some progress in identifying specific markers of both processes. From an aetiological standpoint, perhaps the most vexing issue is to make progress in solving the problem of specificity. A fair bit has been learned about the 'natural history' of GID and it appears to be the case that the prospects for therapeutic intervention are more optimistic during childhood than in adolescence, perhaps not a surprising observation to developmental psychiatrists. Much remains to be learned, however, about the most efficacious forms of treatment and perhaps this will be a goal to be reached in the first decade of the new millennium.

References

- Achenbach, T. & Edelbrock, C. (1983) *Manual for the Child Behavior Checklist and Revised Child Behavior Profile*. University of Vermont, Department of Psychiatry, Burlington, VT.
- Achenbach, T. & Edelbrock, C. (1986) *Manual for the Teacher's Report Form and Teacher Version of the Child Behavior Profile*. University of Vermont, Department of Psychiatry, Burlington, VT.
- Achenbach, T., Howell, C., Quay, H. & Conners, C. (1991) National survey of problems and competencies among four- to sixteen-year-olds. *Monographs of the Society for Research in Child Development* 56 (3, Serial no. 225).
- American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised. American Psychiatric Association, Washington D.C.
- American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn, text revision. American Psychiatric Association, Washington D.C.
- Arbuckle, T., Wilkins, R. & Sherman, G. (1993) Birth weight percentiles by gestational age in Canada. *Obstetrics and Gynecology*, 81, 39–48.
- Bailey, J. & Zucker, K. (1995) Childhood sex-typed behavior and sexual orientation: a conceptual analysis and quantitative review. *Developmental Psychology*, 31, 43–55.
- Bakker, A., van Kesteren, P., Gooren, L. & Bezemer, P. (1993) The prevalence of transsexualism in the Netherlands. *Acta Psychiatrica Scandinavica*, 87, 237–238.
- Bates, J., Bentler, P. & Thompson, S. (1979) Gender-deviant boys compared with normal and clinical control boys. *Journal of Abnormal Child Psychology*, 7, 243–259.

- Bem, D. (1996) Exotic becomes erotic: a developmental theory of sexual orientation. *Psychological Review*, 103, 320–335.
- Berenbaum, S. & Hines, M. (1992) Early androgens are related to childhood sex-typed toy preferences. *Psychological Science*, 3, 203–206.
- Birkenfeld-Adams, A. (1999) *Quality of attachment in young boys with gender identity disorder: a comparison to clinic and nonreferred control boys*. PhD thesis, York University.
- Blanchard, R. & Klassen, P. (1997) H-Y antigen and homosexuality in men. *Journal of Theoretical Biology*, 185, 373–378.
- Blanchard, R., Clemmensen, L. & Steiner, B. (1987) Heterosexual and homosexual gender dysphoria. *Archives of Sexual Behavior*, 16, 139–152.
- Blanchard, R., Zucker, K., Bradley, S. & Hume, C. (1995) Birth order and sibling sex ratio in homosexual male adolescents and probably prehomosexual feminine boys. *Developmental Psychology*, 31, 22–30.
- Bradley, S., Blanchard, R., Coates, S. *et al.* (1991) Interim report of the DSM-IV subcommittee for gender identity disorders. *Archives of Sexual Behavior*, 20, 333–343.
- Bradley, S., Oliver, G., Cherrick, A. & Zucker, K. (1998) Experiment of nurture: ablation penis at 2 months, sex reassignment at 7 months, and a psychosexual follow-up in young adulthood. *Pediatrics*, 102, E91–E95. [Available on the World Wide Web <http://www.pediatrics.org/cgi/content/full/102/1/e9>]
- Campbell, D. & Eaton, W. (1999) Sex differences in the activity level of infants. *Infant and Child Development*, 8, 1–17.
- Caron, C. & Rutter, M. (1991) Comorbidity in child psychopathology: concepts, issues and research strategies. *Journal of Child Psychology and Psychiatry*, 32, 1063–1080.
- Coates, S. & Person, E. (1985) Extreme boyhood femininity: isolated behavior or pervasive disorder? *Journal of the American Academy of Child Psychiatry*, 24, 702–709.
- Cohen-Kettenis, P. (1994) Die Behandlung von Kindern und Jugendlichen mit Geschlechtsidentitätsstörungen an der Universität Utrecht [Clinical management of children and adolescents with gender identity disorders at the University of Utrecht]. *Zeitschrift für Sexualforschung*, 7, 231–239.
- Cohen-Kettenis, P. (1995) Replik auf Bernd Meyenburg's 'Kritik der hormonellen Behandlung Judendlicher mit Geschlechtsidentitätsstörungen' [Rejoinder to Bernd Meyenburg's 'Criticism of hormone treatment for adolescents with gender identity disorders']. *Zeitschrift für Sexualforschung*, 8, 165–167.
- Cohen-Kettenis, P. (2001) Gender identity disorder in DSM? [Letter to the editor]. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40, 391.
- Cohen-Kettenis, P. & van Goozen, S. (1997) Sex reassignment of adolescent transsexuals: a follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36, 263–271.
- Cohen-Kettenis, P. & van Goozen, S. (1998) Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *European Child and Adolescent Psychiatry*, 7, 246–248.
- Corbett, K. (1996) Homosexual boyhood: notes on girlyboys. *Gender and Psychoanalysis*, 1, 429–461.
- Diamond, M. & Sigmundson, H. (1997) Sex reassignment at birth: long-term review and clinical implications. *Archives of Pediatrics and Adolescent Medicine*, 151, 298–304.
- Eaton, W. & Enns, L. (1986) Sex differences in human motor activity level. *Psychological Bulletin*, 100, 19–28.
- Eaton, W. & Von Bargen, D. (1981) Asynchronous development of gender understanding in preschool children. *Child Development*, 52, 1020–1027.
- Ehrhardt, A. & Baker, S. (1974) Fetal androgens, human central nervous system differentiation, and behavior sex differences. In: *Sex Differences in Behavior* (eds R.C. Friedman, R.M. Richart & R.L. Vande Wiele), pp. 33–51. Wiley, New York.
- Fagot, B. (1985) Beyond the reinforcement principle: another step toward understanding sex role development. *Developmental Psychology*, 21, 1097–1104.
- Fergusson, D., Horwood, L. & Beautrais, A. (1999) Is sexual orientation related to mental health problems and suicidality in young people? *Archives of General Psychiatry*, 56, 876–880.
- Gagnon, J. (1990) The explicit and implicit use of the scripting perspective in sex research. *Annual Review of Sex Research*, 1, 1–43.
- Garber, J. & Hollon, S. (1991) What can specificity designs say about causality in psychopathology research? *Psychological Bulletin*, 110, 129–136.
- Garofalo, R., Wolf, R., Kessel, S., Palfrey, J. & DuRant, R. (1999a) The association between health risk behaviors and sexual orientation among a school-based sample of adolescents. *Pediatrics*, 101, 895–902.
- Garofalo, R., Wolf, R., Wissow, L., Woods, E. & Goodman, E. (1999b) Sexual orientation and risk of suicide attempts among a representative sample of youth. *Journal of the American Medical Association*, 281, 487–493.
- Gentile, D. (1993) Just what are sex and gender, anyway? A call for a new terminological standard. *Psychological Science*, 4, 120–122.
- Gibson, L. (1998) *Adult attachment and maternal representations of gender during pregnancy: their impact on the child's subsequent gender-role development*. PhD thesis, City University of New York.
- Golombok, S., Spencer, A. & Rutter, M. (1983) Children in lesbian and single-parent households: psychosexual and psychiatric appraisal. *Journal of Child Psychology and Psychiatry*, 24, 551–572.
- Gooren, L. & Delemarre-van de Waal, H. (1996) The feasibility of endocrine interventions in juvenile transsexuals. *Journal of Psychology and Human Sexuality*, 8, 69–84.
- Goy, R., Bercovitch, F. & McBair, M. (1988) Behavioral masculinization is independent of genital masculinization in prenatally androgenized female rhesus macaques. *Hormones and Behavior*, 22, 552–571.
- Green, R. (1974) *Sexual Identity Conflict in Children and Adults*. Basic Books, New York.
- Green, R. (1987) *The 'Sissy Boy Syndrome' and the Development of Homosexuality*. Yale University Press, New Haven.
- Green, R., Mandel, J., Horvedt, M., Gray, J. & Smith, L. (1986) Lesbian mothers and their children: a comparison with solo parent heterosexual mothers and their children. *Archives of Sexual Behavior*, 15, 167–184.
- Greenberg, M., Speltz, M., DeKlyen, M. & Endriga, M. (1991) Attachment security in preschoolers with and without externalizing behavior problems: a replication. *Development and Psychopathology*, 3, 413–430.
- Haqq, C. & Donahoe, P. (1998) Regulation of sexual dimorphism in mammals. *Physiological Reviews*, 78, 1–33.
- Harry Benjamin International Gender Dysphoria Association (1998) *The Standards of Care for Gender Identity Disorders*, 5th edn. Symposian Publishing, Düsseldorf.
- Herd, G. (1981) *Guardians of the Flute: Idioms of Masculinity*. McGraw-Hill, New York.
- Herman-Jeglinska, A., Dulko, S. & Grabowska, A. (1997) Transsexuality and asexuality: do they share a common origin? In: *Sexual Orientation: Toward Biological Understanding* (eds L. Ellis & L. Ebertz), pp. 163–180. Praeger, Westport, CT.
- Isay, R. (1997) Remove gender identity disorder in DSM. *Psychiatric News* 32, 9, 13.

- Kinsey, A., Pomeroy, W. & Martin, C. (1948) *Sexual Behavior in the Human Male*. W.B. Saunders, Philadelphia.
- Kohlberg, L. (1966) A cognitive-developmental analysis of children's sex-role concepts and attitudes. In: *The Development of Sex Differences* (ed. E.E. Maccoby), pp. 82–173. Stanford University Press, Stanford, CA.
- Lahey, B., McBurnett, K. & Loeber, R. (2000) Are attention-deficit/hyperactivity disorder and oppositional defiant disorder developmental precursors to conduct disorder? In: *Handbook of Developmental Psychopathology* (eds A.J. Sameroff, M. Lewis & S.M. Miller), 2nd edn, pp. 431–446. Kluwer Academic/Plenum Publishers, New York.
- Lalumière, M., Blanchard, R. & Zucker, K. (2000) Sexual orientation and handedness in men and women: a meta-analysis. *Psychological Bulletin*, 126, 575–592.
- Laumann, E., Gagnon, J., Michael, R. & Michaels, S. (1994) *The Social Organization of Sexuality: Sexual Practices in the United States*. University of Chicago Press, Chicago.
- Lothstein, L. (1983) *Female-to-male Transsexualism: Historical, Clinical, and Theoretical Issues*. Routledge & Kegan Paul, Boston.
- Lytton, H. & Romney, D. (1991) Parents' differential socialization of boys and girls: a meta-analysis. *Psychological Bulletin*, 109, 267–296.
- Maccoby, E. (1988) Gender as a social category. *Developmental Psychology*, 24, 755–765.
- Marantz, S. & Coates, S. (1991) Mothers of boys with gender identity disorder: a comparison of matched controls. *Journal of the American Academy of Child and Adolescent Psychiatry*, 30, 310–315.
- Meyenburg, B. (1994) Kritik der hormonellen Behandlung Jugendlicher mit Geschlechtsidentitätsstörungen [Criticisms of hormone treatment for adolescents with gender identity disorders]. *Zeitschrift für Sexualforschung*, 7, 343–349.
- Meyer, I. (1995) Minority stress and mental health in gay men. *Journal of Health and Social Behavior*, 36, 38–56.
- Meyer-Bahlburg, H. (1984) Psychoendocrine research on sexual orientation: current status and future options. *Progress in Brain Research*, 61, 375–398.
- Meyer-Bahlburg, H. (1985) Gender identity disorder of childhood: introduction. *Journal of the American Academy of Child Psychiatry*, 24, 681–683.
- Meyer-Bahlburg, H. (1994) Intersexuality and the diagnosis of gender identity disorder. *Archives of Sexual Behavior*, 23, 21–40.
- Meyer-Bahlburg, H. (1999a) Gender assignment and reassignment in 46,XY pseudohermaphroditism and related conditions. *Journal of Clinical Endocrinology and Metabolism*, 84, 3455–3458.
- Meyer-Bahlburg, H. (1999b) Review of 'The last time I wore a dress: a memoir'. *Archives of Sexual Behavior*, 28, 431–434.
- Meyer-Bahlburg, H., Gruen, R., New, M. *et al.* (1996) Gender change from female to male in classical congenital adrenal hyperplasia. *Hormones and Behavior*, 30, 319–332.
- Migeon, C. & Wisniewski, A. (1998) Sexual differentiation: from genes to gender. *Hormone Research*, 50, 245–251.
- Minter, S. (1999) Diagnosis and treatment of gender identity disorder in children. In: *Sissies and Tomboys: Gender Nonconformity and Homosexual Childhood* (ed. M. Rottnek), pp. 9–33. New York University Press, New York.
- Mitchell, J. (1991) *Maternal influences on gender identity disorder in boys: searching for specificity*. PhD thesis, York University.
- Money, J. (1955) Hermaphroditism, gender and precocity in hyperadrenocorticism: psychologic findings. *Bulletin of the Johns Hopkins Hospital*, 96, 253–264.
- Money, J. (1975) Ablatio penis: normal male infant sex-reassigned as a girl. *Archives of Sexual Behavior*, 4, 65–71.
- Money, J. (1985) The conceptual neutering of gender and the criminalization of sex. *Archives of Sexual Behavior*, 14, 279–290.
- Money, J., Hampson, J. & Hampson, J. (1957) Imprinting and the establishment of gender role. *Archives of Neurology and Psychiatry*, 77, 333–336.
- Newman, L. (1970) Transsexualism in adolescence: problems in evaluation and treatment. *Archives of General Psychiatry*, 23, 112–121.
- Pleak, R. (1999) Ethical issues in diagnosing and treating gender-dysphoric children and adolescents. In: *Sissies and Tomboys: Gender Nonconformity and Homosexual Childhood* (ed. M. Rottnek), pp. 34–51. New York University Press, New York.
- Pleak, R., Meyer-Bahlburg, H., O'Brien, J., Bowen, H. & Morganstein, A. (1989) Cross-gender behavior and psychopathology in boy psychiatric outpatients. *Journal of the American Academy of Child and Adolescent Psychiatry*, 28, 385–393.
- Qazi, Q. & Thompson, M. (1971) Birthweight in congenital virilizing adrenal hyperplasia. *Archives of Disease in Childhood*, 46, 350–352.
- Remafedi, G., French, S., Story, M., Resnick, M. & Blum, R. (1998) The relationship between suicide risk and sexual orientation: results of a population-based study. *American Journal of Public Health*, 88, 57–60.
- Richardson, J. (1996) Setting limits on gender health. *Harvard Review of Psychiatry*, 4, 49–53.
- Richardson, J. (1999) Response: finding the disorder in gender identity disorder. *Harvard Review of Psychiatry*, 7, 43–50.
- Roberts, C., Green, R., Williams, K. & Goodman, M. (1987) Boyhood gender identity development: a statistical contrast of two family groups. *Developmental Psychology*, 23, 544–557.
- Rosen, R. & Beck, J. (1988) *Patterns of Sexual Arousal: Psychophysiological Processes and Clinical Applications*. Guilford Press, New York.
- Ross, M. (1983) *The Married Homosexual Man: A Psychological Study*. Routledge & Kegan Paul, Boston.
- Ruble, D. & Martin, C. (1998) Gender development. In: *The Handbook of Child Psychology*, Vol. 3. *Social, Emotional, and Personality Development* (series ed. W. Damon; volume ed. N. Eisenberg), 5th edn, pp. 933–1016. Wiley, New York.
- Sandberg, D., Meyer-Bahlburg, H., Ehrhardt, A. & Yager, T. (1993) The prevalence of gender-atypical behavior in elementary school children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 32, 306–314.
- Saudino, K. & Eaton, W. (1991) Infant temperament and genetics: an objective twin study of motor activity level. *Child Development*, 62, 1167–1174.
- Scholinski, D. (1997) *The Last Time I Wore a Dress: A Memoir*. Riverhead Books, New York.
- Sedgwick, E. (1991) How to bring your kids up gay. *Social Text*, 9, 18–27.
- Spitzer, R. & Wakefield, J. (1999) DSM-IV diagnostic criterion for clinical significance: does it help solve the false positive problem? *American Journal of Psychiatry*, 156, 1856–1864.
- Stoller, R. (1964) The hermaphroditic identity of hermaphrodites. *Journal of Nervous and Mental Disease*, 139, 453–457.
- Stoller, R. (1967) It's only a phase': femininity in boys. *Journal of the American Medical Association*, 201, 314–315.
- Stoller, R. (1975) *Sex and Gender*, Vol. 2, *The Transsexual Experiment*. Hogarth Press, London.
- Tasker, F. & Golombok, S. (1997) *Growing Up in a Lesbian Family: Effects on Child Development*. Guilford Press, New York.
- Vilain, E. & McCabe, E. (1998) Mammalian sex determination: from gonads to brain. *Molecular Genetics and Metabolism*, 65, 74–84.
- Weeks, J. (1991) *Against Nature: Essays on History, Sexuality, and Identity*. Rivers Oram Press, London.

- Weiner, B. (1993) On sin versus sickness: a theory of perceived responsibility and social motivation. *American Psychologist*, 48, 957–965.
- Weisz, J. & Weiss, B. (1991) Studying the ‘referability’ of child clinical problems. *Journal of Consulting and Clinical Psychology*, 59, 266–273.
- Willerman, L. (1973) Activity level and hyperactivity in twins. *Child Development*, 44, 288–293.
- Wolfe, S. (1990) *Psychopathology and psychodynamics of parents of boys with a gender identity disorder of childhood*. PhD thesis, City University of New York.
- World Health Organization (1992) *International Statistical Classification of Diseases and Related Health Problems*, 10th revision. World Health Organization, Geneva.
- de Zegher, F., Francois, L., Boehmer, A. *et al.* (1998) Androgens and fetal growth. *Hormone Research*, 50, 243–244.
- Zoccolillo, M., Pickles, A., Quinton, D. & Rutter, M. (1992) The outcome of childhood conduct disorder: implications for defining adult personality disorder and conduct disorder. *Psychological Medicine*, 22, 971–986.
- Zucker, K. (1985) Cross-gender-identified children. In: *Gender Dysphoria: Development, Research, Management* (ed. B.W. Steiner), pp. 75–174. Plenum Press, New York.
- Zucker, K. (1990) Gender identity disorders in children: clinical descriptions and natural history. In: *Clinical Management of Gender Identity Disorders in Children and Adults* (eds R. Blanchard & B.W. Steiner), pp. 1–23. American Psychiatric Press, Washington D.C.
- Zucker, K. (1992) Gender identity disorder. In: *Child Psychopathology: Diagnostic Criteria and Clinical Assessment* (eds S.R. Hooper, G.W. Hynd & R.E. Mattison), pp. 305–342. Erlbaum, Hillsdale, NJ.
- Zucker, K. (1996) Pathological gender mourning in mothers of boys with gender identity disorder: clinical evidence and some psychocultural hypotheses. Paper presented at the Meeting of the Society for Sex Therapy and Research, Miami Beach.
- Zucker, K. (1999a) Commentary on Richardson’s (1996) ‘Setting Limits on Gender Health’. *Harvard Review of Psychiatry*, 7, 37–42.
- Zucker, K. (1999b) Intersexuality and gender identity differentiation. *Annual Review of Sex Research*, 10, 1–69.
- Zucker, K. (1999c) Gender identity disorder in the DSM-IV [Letter to the editor]. *Journal of Sex and Marital Therapy*, 25, 5–9.
- Zucker, K. (2000a) Gender identity disorder. In: *Handbook of Developmental Psychopathology* (eds A.J. Sameroff, M. Lewis & S.M. Miller), 2nd edn, pp. 671–686. Kluwer Academic/Plenum, New York.
- Zucker, K. (2000b) Commentary on Walters and Whitehead’s (1997) ‘Anorexia Nervosa in a Young Boy with Gender Identity Disorder of Childhood: A Case Report’. *Clinical Child Psychology and Psychiatry*, 5, 232–238.
- Zucker, K. (2001) Gender identity disorder in children and adolescents. In: *Treatments of Psychiatric Disorders*, Vol. 2 (ed. G.O. Gabbard), 3rd edn, pp. 2069–2094. American Psychiatric Press, Washington, DC.
- Zucker, K. & Bradley, S. (1995) *Gender Identity Disorder and Psychosexual Problems in Children and Adolescents*. Guilford Press, New York.
- Zucker, K. & Bradley, S. (2000) Gender identity disorder. In: *Handbook of Infant Mental Health* (ed. C.H. Zeanah), 2nd edn, pp. 412–424. Guilford Press, New York.
- Zucker, K., Bradley, S., Doering, R. & Lozinski, J. (1985) Sex-typed behavior in cross-gender-identified children: stability and change at a one-year follow-up. *Journal of the American Academy of Child Psychiatry*, 24, 710–719.
- Zucker, K., Bradley, S. & Ipp, M. (1993a) Delayed naming of a newborn boy: relationship to the mother’s wish for a girl and subsequent cross-gender identity in the child by the age of two. *Journal of Psychology and Human Sexuality*, 6, 57–68.
- Zucker, K., Bradley, S., Lowry Sullivan, C., Kuksis, M., Birkenfeld-Adams, A. & Mitchell, J. (1993b) A gender identity interview for children. *Journal of Personality Assessment*, 61, 443–456.
- Zucker, K., Green, R., Garofano, C. *et al.* (1994) Prenatal gender preference of mothers of feminine and masculine boys: relation to sibling sex composition and birth order. *Journal of Abnormal Child Psychology*, 22, 1–13.
- Zucker, K., Bradley, S. & Lowry Sullivan, C. (1996a) Traits of separation anxiety in boys with gender identity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35, 791–798.
- Zucker, K., Bradley, S., Oliver, G., Blake, J., Fleming, S. & Hood, J. (1996b) Psychosexual development of women with congenital adrenal hyperplasia. *Hormones and Behavior*, 30, 300–318.
- Zucker, K., Bradley, S. & Sanikhani, M. (1997a) Sex differences in referral rates of children with gender identity disorder: some hypotheses. *Journal of Abnormal Child Psychology*, 25, 217–227.
- Zucker, K., Green, R., Coates, S. *et al.* (1997b) Sibling sex ratio of boys with gender identity disorder. *Journal of Child Psychology and Psychiatry*, 38, 543–551.
- Zucker, K., Blanchard, R., Cavacas, A., Bradley, S., Paterson, A. & Schachter, D. (1999a) *Birthweight in children with gender identity disorder*. Poster presented at the meeting of the International Academy of Sex Research, Stony Brook, New York.
- Zucker, K., Bradley, S., Kuksis, M. *et al.* (1999b) Gender constancy judgments in children with gender identity disorder: evidence for a developmental lag. *Archives of Sexual Behavior*, 28, 475–502.
- Zucker, K., Beaulieu, N., Bradley, S., Grimshaw, G. & Wilcox, A. (2001) Handedness in boys with gender identity disorder. *Journal of Child Psychology and Psychiatry*, 42, 767–776.
- Zucker, K., Owen, A., Bradley, S. & Ameeriar, L. (in press) Gender-dysphoric children and adolescents: a comparative analysis of demographic characteristics and behavioral problems. *Clinical Child Psychology and Psychiatry*.

EXHIBIT H

Moral Complicity with Evil

Moral complicity with evil is culpable association with or participation in wrongful acts. Evil is defined as anything immoral or wrong based on Biblical principles. Questions about moral complicity with evil can arise in regard to an individual's relationship to or involvement with past, present or future evil.

Moral complicity may occur with the use of information, technology or materials obtained through immoral means. This complicity may involve using, rewarding, perpetuating, justifying, or ignoring past or present evil. Moral complicity may involve enabling or facilitating future immoral actions of patients or professionals.

We must strive to never commit evil ourselves, nor should we participate in or encourage evil by others. While it may be impossible at times to completely distance ourselves from the evil actions of others, we are responsible to determine whether our action is appropriately distanced or inappropriately complicit. This determination is based on the revealed Word of God. In the absence of clear Biblical teaching, this determination is based on conscience as informed by the Holy Spirit, using but recognizing the innately fallible nature of human reason and prudence.

BIBLICAL GUIDELINES

1. We must avoid every kind of evil (I Thessalonians 5:22)
2. We may never do evil that good may come. (Romans 3: 8)
3. We must hate and oppose evil. (Romans 12: 9)
4. We should separate ourselves from evil. (II Corinthians 6: 17)
5. We cannot totally separate ourselves from evil. (I Corinthians 5: 9 & 10)
6. We should overcome evil with good. (Romans 12: 21)
7. We should seek wisdom. (James 1: 2-5)

APPLICATIONS

1. Intent. Our motives must be always to promote good, never evil.
2. Magnitude. Some evil acts are so heinous that any association with them is unacceptable.
3. Timing. Passage of time may diminish complicity with prior evil acts, though it does not diminish the evil nature of the original act.
4. Proximity. A greater degree of association with an evil act increases culpability.
5. Knowledge. Knowledge that an original act was evil and knowledge that a subsequent act is associated with that act are both required for culpability.
6. Certitude. A greater degree of certainty that the original action was evil increases complicity.

CONCLUSIONS

CMDA believes moral complicity with evil does not exist when all the following conditions are satisfied:

1. our intent is for good;
2. the association with the past or present evil is sufficiently uncertain, or the act is sufficiently distanced from the original evil act; and
3. the action does not reward, perpetuate, justify, cooperate with, or ignore the original evil.

REFERENCES

1. For example, the potential for moral complicity exists in the use of (a) research data from unethical experiments, (b) textbooks or drawings made using tortured or executed prisoners, (c) vaccines made from aborted fetal tissue, etc.
- 2 For example, enabling a patient to engage in immoral activity (sexual immorality, suicide, drug abuse, criminal activity) or facilitating an immoral procedure by another professional (cloning; genetic enhancement; referral for or assisting in abortion or unethical reproductive technologies) may involve some culpability.

*Approved by the House of Representatives
Passed unanimously.
June 11, 2004. San Antonio, Texas.*

EXHIBIT I

April 19, 2016

Re: Support for the Conscience Protection Act of 2016 (H.R. 4828)

Dear Representative:

We represent millions of Americans and tens of thousands of health care professionals with a profound concern about abortion, and particularly about the conscience rights of health care professionals and facilities. Federal laws protecting conscientious objection to abortion have been approved for decades by Congresses and Presidents of both parties. Even many “pro-choice” Americans realize that the logic of their position requires them to respect a choice *not* to be involved in abortion. Yet it is increasingly clear that the current laws offer far less protection in practice than in theory.

For example, the state of California in 2014 began demanding that all health plans under the jurisdiction of the state’s Department of Managed Health Care -- even those purchased by churches and other religious organizations -- cover elective abortions for any reason, including late-term abortions and those performed for reasons of “sex selection.” No exemption of any kind is allowed. This policy flagrantly violates the Weldon amendment, which has been part of the annual Labor/HHS appropriations laws for over a decade. Yet the HHS Office for Civil Rights has not acted on the complaints that were filed against this coercive mandate over a year ago, despite Congress’s demand for swift action in its report language accompanying the final Labor/HHS appropriations acts for FY 2015 and FY 2016. Moreover, an attempt by that agency to enforce Weldon could revive a legal challenge to this law by California and other states, based on the law’s broad denial of all Labor/HHS funds to a governmental body that violates it. And Weldon and other federal conscience laws do not authorize a “private right of action” allowing the victims of discrimination to sue on their own behalf, and allowing courts to take measured action to end this discrimination.

Such loopholes in current laws are addressed by the Conscience Protection Act (H.R. 4828), introduced on March 22 by Reps. John Fleming, M.D. (R-LA) and Vicky Hartzler (R-MO). This Act is very similar to the Abortion Non-Discrimination provision that for the last three years has been part of the House’s Labor/HHS appropriations bills. It takes the core policy of Weldon -- protecting those who decline to perform, pay for, refer for, or provide coverage for abortion -- and writes it into permanent law. It clarifies the protections of Weldon, and adds a private right of action to enforce this law and other longstanding conscience laws on abortion. This will help nurses and other health professionals like Cathy DeCarlo, threatened with loss of their careers and livelihoods if they do not assist in abortions, whose cases have sometimes languished for years at the HHS Office for Civil Rights.

Notably, there have been no serious efforts in Congress to repeal or weaken these current laws for many years, and President Obama and his Department of Health and Human Services have voiced active support for all of them. All we need to agree on is that these widely supported laws should be effective and have a workable and timely means of enforcement.

This would mean almost no change in the substantive policy of Congress; but it would be an enormous step forward in assuring Americans who serve the sick and needy that they can do so without being forced by government to violate their most deeply held convictions on respect for innocent human life. We urge you to give a high priority to the passage into law of the Conscience Protection Act this year. Please support and co-sponsor this important legislation.

Sincerely,

United States Conference of Catholic Bishops

Christian Medical Association

Catholic Medical Association

National Council of Catholic Women

March for Life Education and Defense Fund

American College of Pediatricians

Christ Medicus Foundation

American Association of Pro-Life Obstetricians and Gynecologists

Susan B. Anthony List

National Catholic Bioethics Center

Family Research Council

Americans United for Life Action

National Association of Pro-Life Nurses

The National Association of Catholic Nurses – U.S.A.

The Catholic Benefits Association

Catholic Healthcare International

National Right to Life Committee

American Academy of Fertility Care Professionals

National Association of Evangelicals

Southern Baptist Ethics & Religious Liberty Commission

Sacred Heart Mercy Health Care Centers (Michigan and Minnesota)

Knights of Columbus

California Nurses for Ethical Standards

Association of American Physicians and Surgeons

Institute for Youth Development

Alliance Defending Freedom

EXHIBIT J

May 2011: National poll shows majority support healthcare conscience rights, conscience law

Highlights of *the polling company, inc.* Phone Survey of the American Public

On May 3, 2011, the Christian Medical Association and the Freedom2Care coalition released the results of a nationwide, scientific poll conducted April 29-May 1, 2011 by the polling company™, inc./ WomanTrend. Survey of 1000 American Adults, Field Dates: April 29-May 1, 2011, Margin of Error=±3.1.

1. **77%** of American adults surveyed said it is either "very" or "somewhat" important to them that "that healthcare professionals in the U.S. are **not forced to participate** in procedures or practices to which they have **moral objections**." **16%** said it is not important.

ALL		PRO- CHOICE (n=465)	PRO- LIFE (n=461)
77%	Total important (net)	68%	85%
52%	Very important	42%	64%
25%	Somewhat important	26%	21%
16%	Total not important (net)	24%	8%
8%	Not too important	11%	5%
8%	Not at all important	13%	3%
8%	Do not know/depends	8%	6%
1%	Refused	*	

2. **50%** of American adults surveyed "strongly" or "somewhat" support "a **law** under which federal agencies and other government bodies that receive federal funds could **not discriminate** against hospitals and health care professionals who **decline to participate in abortions**." **35%** opposed.

ALL		PRO- CHOICE (n=465)	PRO- LIFE (n=461)
50%	Total support (net)	45%	58%
29%	Strongly support	20%	40%
21%	Somewhat support	25%	18%
35%	Total oppose (net)	43%	32%
14%	Somewhat oppose	20%	10%
21%	Strongly oppose	23%	22%
7%	It depends/need more info.	7%	5%
7%	Do not know	6%	5%
1%	Refused	1%	1%

April, 2009: Two National Polls¹ Reveal Broad Support for Conscience Rights in Health Care

Highlights of *the polling company, inc.* Phone Survey of the American Public

39% Democrat • 33% Republican • 22% Independent

1. **88%** of American adults surveyed said it is either “very” or “somewhat” **important to them that they share a similar set of morals as their doctors**, nurses, and other healthcare providers.
2. **87%** of American adults surveyed believed it is important to “make sure that healthcare professionals in America are **not forced to participate** in procedures and practices to which they have moral objections.”
3. Support for the conscience protection regulation (rule finalized Dec. 2008):
 - **63% support conscience protection regulation**
 - 28% oppose conscience protection regulation
4. Support for Obama administration proposal to eliminate the new conscience protection regulation:
 - 30% support Obama administration proposal
 - **62% oppose Obama administration proposal**
5. Likelihood of voting for current Member of Congress who supported eliminating the conscience rule:
 - 25% more likely to vote for Member who supported eliminating rule
 - **54% less likely to vote for Member who supported eliminating rule**
6. "In 2004 the Hyde-Weldon Amendment was passed. It ruled that taxpayer funds must not be used by governments and government-funded programs to discriminate against hospitals, health insurance plans, and healthcare professionals who decline to participate in abortions. Do you support or oppose this law?"
 - **58% support Hyde-Weldon Amendment**
 - 31% oppose Hyde-Weldon Amendment

Highlights of Online Survey of Faith-Based Professionals

2,865 faith-based healthcare professionals

1. **Over nine of ten (91%)** faith-based physicians agreed, "I would **rather stop practicing medicine** altogether than be forced to violate my conscience."
2. **32%** of faith-based healthcare professionals report having "been **pressured to refer a patient** for a procedure to which [they] had moral, ethical, or religious objections."
3. **39%** of faith-based healthcare professionals have “experienced pressure from or **discrimination by faculty** or administrators based on [their] moral, ethical, or religious beliefs”
4. **20%** of faith-based medical students say they are "**not pursuing a career in Obstetrics or Gynecology**" because of perceived discrimination and coercion in that field.

¹ Results of both 2009 surveys released April 8. On behalf of the Christian Medical Association, the polling companyTM, inc./ WomanTrend conducted a nationwide survey of 800 American adults. Field Dates: March 23 -25, 2009. The overall margin of error for the survey is ± 3.5% at a 95% confidence interval. The polling companyTM, inc./ WomanTrend also conducted an online survey of members of faith-based organizations, fielded March 31, 2009 to April 3, 2009. It was completed by 2,298 members of the Christian Medical Association, 400 members of the Catholic Medical Association, 69 members of the Fellowship of Christian Physicians Assistants, 206 members of the Christian Pharmacists Fellowship International, and 8 members of Nurses Christian Fellowship. <http://www.freedom2care.org/learn/page/surveys>

April 2009 Phone Survey of the American Public

Americans of all characteristics and politics seek shared values with healthcare professionals.

Fully 88% of American adults surveyed said it is either “very” or “somewhat” important to them that they enjoy a similar set of morals as their doctors, nurses, and other healthcare providers. Intensity was strong, as 63% described this as “very” important while at the other end of the spectrum, just 6% said it is “not at all important,” a ratio of more than 10-to-1.

Voters will punish politicians who fail to defend healthcare providers’ conscience rights.

Finally, when asked how they would view their Member of Congress if he or she voted against conscience protection rights, 54% indicated they would be less likely to back their United States Representative. In fact, 36% said they would be much less likely, a figure three times greater than the 11 % who said they would be much more likely. Furthermore, 43% of respondents who said they voted for President Obama indicated that they would be less inclined to back a Member of Congress if he or she opposed conscience protection rights.

Healthcare providers’ conscience protections are viewed as an inalienable right.

A sizable 87% of American adults surveyed believed it is important to “make sure that healthcare professionals in America are not forced to participate in procedures and practices to which they have moral objections.” 65% of respondents considered it very essential. Also joining with these majorities were 95% of respondents who self-identified as “pro-life,” 78% who considered themselves “pro-choice,” 94% who voted for Senator McCain in November 2008 and 80% who cast a ballot for (now) President Obama.

Americans oppose forcing healthcare providers to act against their consciences...

A majority (57%) of American adults opposed regulations “that require medical professionals to perform or provide procedures to which they have moral or ethical objections.” In contrast, 38% favored such rules. A full 40% strongly objected to the rules while just 19% strongly backed them. A majority of conservative Republicans (69%), moderate Republicans (69%), and conservative Democrats (59%), as well as the plurality of liberal/moderate Democrats (49%), joining together to reject policies to that require doctors and nurses to act against their personal moral code or value set.

...Support laws that protect them from doing so...

Without any names or political parties being mentioned, support for the new conscience protection rule outpaced opposition by a margin of more than 2-to-1 (63% vs. 28%). Intensity favored the rule, with 42% strongly backing it and 19% strongly rejecting it. Endorsements for the rule spanned demographic and political spectra, with majorities in all cohorts offering their support. In fact, even 56% of adults who said they voted for President Obama last fall and 60% of respondents who self-identified as “pro-choice” said they favor this two-month old conscience protection rule.

... And oppose any efforts to remove such rules.

Opposition to revocation of the conscience protection rule outpaced support by a margin of more than 2- to-1 (62% vs. 30%). Intensity favored retention of the rule (44% strongly opposing rescission versus 17% strongly supporting it). There was consistent demographic alignment and cohesiveness across political lines, as 52% of self-identified Democrats, 67% of self-identified Independents, and 73% of self- identified Republicans, as well as 50% of liberals, 65% of moderates, and 69% of conservatives also opposed nullification. A narrow majority (53%) of people who considered themselves to be “pro-choice” opposed rescission. Notably, a small number

Online Survey of Faith-Based Medical Professionals

1. Medical access will suffer if doctors are forced to act against their moral and ethical codes.

In the survey of 2,865 members of faith-based organizations, doctors and other medical professionals voiced their concerns that serious consequences could occur if doctors are forced to participate in or perform practices to which they have moral or ethical objections. Nearly three-quarters (74%) believed that elimination of the conscience protection could result in “fewer doctors practicing medicine,” 66% predicted “decreased access to healthcare providers, services, and/or facilities for patients in low-income areas,” 64% surmised “decreased access to healthcare providers, services, and/or facilities for patients in rural areas,” and 58% hypothesized “fewer hospitals providing services.”

Asked how rescission of the rule would affect them personally, 82% said it was either “very” or “somewhat” likely that they personally would limit the scope of their practice of medicine. This was true of 81% of medical professionals who practice in rural areas and 86% who work full-time serving poor and medically-underserved populations.

The conscience protection rule is fundamental and necessary in the medical profession.

Fully 97% of members who participated in the survey supported the two-month-old conscience protection clause and 96% objected to rescission of the rule. 91% of physicians agreed, "I would rather stop practicing medicine altogether than be forced to violate my conscience." The Department of Health and Human Services has asked whether the objectives of the conscience protection rule can be achieved “through non-regulatory means, such as outreach and education.” Nearly nine-in-ten (87%) members surveyed – those who are on the ground, in hospitals and clinics across the country – felt “outreach and education” alone were insufficient to accomplish the goal. Ninety-two percent declared the codification of conscience protection to be necessary (83% “very” and 9% “somewhat”) based on their knowledge of “discrimination in healthcare on the basis of conscience, religious, and moral values.”

Discrimination is widespread in education and professional practice.

Asked to assess their educational experiences:

- 39% have “experienced pressure from or discrimination by faculty or administrators based on [their] moral, ethical, or religious beliefs”
- 33% have “considered not pursuing a career in a particular medical specialty because of attitudes prevalent in that specialty that is not considered tolerant of [their] moral, ethical or religious beliefs.”
- 23% have “experienced discrimination during the medical school or residency application and interview process because of [their] moral, ethical or religious beliefs.”

Asked to assess their professional experiences:

- 32% have “been pressured to refer a patient for a procedure to which [they] had moral, ethical, or religious objections.”
- 26% have “been pressured to write a prescription for a medication to which [they] had moral, ethical, or religious objections.”
- 17% have “been pressured to participate in training for a procedure to which [they] had moral, ethical, or religious objections.”
- 12% have “been pressured to perform a procedure to which [they] had moral, ethical, or religious objections.”

- 20% of students surveyed agreed with the statement, "I am **not pursuing a career in Obstetrics or Gynecology** mainly because I do not want to be forced to compromise my moral, ethical, or religious beliefs by being required to perform or participate in certain procedures or provide certain medications."
- **96%** of medical students support (90% "Strongly Support") the conscience protection regulation.
- 32% of medical students say they "have experienced pressure from or **discrimination by faculty** or administrators based on your moral, ethical, or religious beliefs."

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
WICHITA FALLS DIVISION

FRANCISCAN ALLIANCE, INC., *et al.*,

Plaintiffs,

v.

SYLVIA BURWELL, *et al.*,

Defendants.

No. 7:16-cv-00108-O

**Declaration of Dr. Robert P.
Hoffman**

1. My name is Dr. Robert P. Hoffman. I am over the age of 21 and am capable of making this declaration pursuant to 28 U.S.C. §1746. I have not been convicted of a felony or crime involving dishonesty.

2. The facts contained herein are within my personal knowledge and medical judgment. If I were called upon to testify to these facts, I could and would competently do so.

3. I obtained my medical degree from Ohio State University College of Medicine. I am the Program Director of the Pediatric, Endocrinology, Diabetes, and Metabolism Division at Nationwide Children's Hospital. I am also a Professor at Ohio State University. I have served on the Ethics Council of the Pediatric Endocrine Society. I have published over 70 peer-reviewed articles, generally dealing with diabetes and cardiovascular endocrinology issues.

4. A significant amount of my patients are Medicaid patients. Because of my pediatric specialty, virtually all of the patients that I see are infants or children.

5. I have been a member of CMDA for approximately 20 years. I am part of CMDA for a number of reasons, including because I believe in Christian medical

practice. CMDA's ethical statements are consistent with my own medical and religious beliefs.

6. I believe all patients should be treated with dignity and compassion, and I currently treat transgender patients who have type 1 diabetes. I give my transgender patients the same loving and compassionate medical care I give all my patients.

7. As part of my normal medical practice, I offer puberty blocking medication to children who have precocious puberty, meaning that puberty begins earlier than is healthy for that child. Puberty blocking medication is provided to help the child avoid health issues until the child's body is ready for the normal onset of puberty. For example, I have prescribed this medication to a child experiencing precocious puberty as young as 3 or 4 years of age. If I were asked to offer puberty blocking medication to a child referred to me for gender dysphoria, to prevent the natural onset of that child's puberty and to continue to prevent the normal hormone production in that individual as the child ages, I would not be able to do so in light of my medical judgment and religious beliefs.

8. As part of my normal medical practice, I also prescribe hormones to children with medical issues such as hypogonadism, where the child's body is not naturally producing the proper amount of hormones they need to develop. If I were asked to offer hormone replacement therapy to a child referred to me for gender dysphoria, which would involve prescribing estrogen to natal boys or testosterone to natal girls, I would not be able to do so in light of my medical judgment and religious beliefs.

9. Based on my experience as a doctor and my familiarity with the medical literature, my medical judgment is that gender transition procedures, particularly for children, are experimental and pose grave risks. For example, the vast majority of children who experience gender dysphoria will not continue to experience gender

dysphoria after adolescence (up to 94% in one set of studies cited by WPATH, and up to 88% in another set of studies cited by WPATH). *See* Exhibit A, World Professional Association for Transgender Health (WPATH), *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People* (7th ed. 2012).

10. Thus, efforts to use hormones or medication to postpone or prevent puberty, or to align gender characteristics opposite to genetic sex prior to adulthood, can be harmful. Medication prescribed to a previously biologically healthy child for the purpose of blocking puberty inhibits normal growth and fertility. Continuation of cross-sex hormones, such as estrogen and testosterone, during adolescence is associated with increased health risks including, but not limited to, high blood pressure, blood clots, stroke, and some types of cancer. This type of hormone therapy can also result in some irreversible physical consequences for the child, such as a permanently lowered voice and increased facial hair for a natal girl. I would express these and other medical risks to caution patients against undergoing gender transition.

11. Performing gender transition procedures on young children would not only contradict my medical judgment, it would violate my religious beliefs. I believe that human beings are created in the image of God as male or female and that it is both impossible and contrary to human dignity to seek to change them a different biological gender. My religious beliefs also inspire me to serve every patient with love and dignity, and to only offer treatments to my patients that I believe are helpful rather than harmful.

12. I treat my patients at a hospital that has always accommodated my beliefs. That accommodation is quite easy, as I work with other pediatric endocrinologists who are able to perform gender transition procedures for children, and so there is no

need for me to do so. I want to continue being accommodated, but am very concerned that the new Rule will prohibit my hospital from doing so.

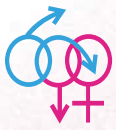
I declare under penalty of perjury that the foregoing is true and correct.

Executed on October 20, 2016.

A handwritten signature in dark ink, appearing to read "Robert P. Hoffman MD", is written over a horizontal line.

DR. ROBERT P. HOFFMAN

EXHIBIT A



WPATH WORLD PROFESSIONAL
ASSOCIATION for
TRANSGENDER HEALTH

Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People

The World Professional Association for Transgender Health



Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People

Eli Coleman, Walter Bockting, Marsha Botzer, Peggy Cohen-Kettenis, Griet DeCuypere, Jamie Feldman, Lin Fraser, Jamison Green, Gail Knudson, Walter J. Meyer, Stan Monstrey, Richard K. Adler, George R. Brown, Aaron H. Devor, Randall Ehrbar, Randi Ettner, Evan Eyler, Rob Garofalo, Dan H. Karasic, Arlene Istar Lev, Gal Mayer, Heino Meyer-Bahlburg, Blaine Paxton Hall, Friedmann Pfäfflin, Katherine Rachlin, Bean Robinson, Loren S. Schechter, Vin Tangpricha, Mick van Trotsenburg, Anne Vitale, Sam Winter, Stephen Whittle, Kevan R. Wylie & Ken Zucker

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7th Version¹ | www.wpath.org

ISBN: X-XXX-XXXXX-XX

¹ This is the seventh version of the *Standards of Care* since the original 1979 document. Previous revisions were in 1980, 1981, 1990, 1998, and 2001. Version seven was published in the *International Journal of Transgenderism*, 13(4), 165–232. doi:10.1080/15532739.2011.700873

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Purpose and Use of the *Standards of Care*

The World Professional Association for Transgender Health (WPATH)^I is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health. The vision of WPATH is a world wherein transsexual, transgender, and gender-nonconforming people benefit from access to evidence-based health care, social services, justice, and equality.

One of the main functions of WPATH is to promote the highest standards of health care for individuals through the articulation of *Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People*. The SOC are based on the best available science and expert professional consensus.^{II} Most of the research and experience in this field comes from a North American and Western European perspective; thus, adaptations of the SOC to other parts of the world are necessary. Suggestions for ways of thinking about cultural relativity and cultural competence are included in this version of the SOC.

The overall goal of the SOC is to provide clinical guidance for health professionals to assist transsexual, transgender, and gender-nonconforming people with safe and effective pathways to achieving lasting personal comfort with their gendered selves, in order to maximize their overall health, psychological well-being, and self-fulfillment. This assistance may include primary care, gynecologic and urologic care, reproductive options, voice and communication therapy, mental health services (e.g., assessment, counseling, psychotherapy), and hormonal and surgical treatments. While this is primarily a document for health professionals, the SOC may also be used by individuals, their families, and social institutions to understand how they can assist with promoting optimal health for members of this diverse population.

WPATH recognizes that health is dependent upon not only good clinical care but also social and political climates that provide and ensure social tolerance, equality, and the full rights of citizenship. Health is promoted through public policies and legal reforms that promote tolerance and equity

I Formerly the Harry Benjamin International Gender Dysphoria Association

II The *Standards of Care (SOC)*, Version 7, represents a significant departure from previous versions. Changes in this version are based upon significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for transsexual, transgender, and gender-nonconforming people beyond hormone therapy and surgery (Coleman, 2009a, b, c, d).

for gender and sexual diversity and that eliminate prejudice, discrimination, and stigma. WPATH is committed to advocacy for these changes in public policies and legal reforms.

The *Standards of Care* Are Flexible Clinical Guidelines

The SOC are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).

As in all previous versions of the SOC, the criteria put forth in this document for hormone therapy and surgical treatments for gender dysphoria are clinical guidelines; individual health professionals and programs may modify them. Clinical departures from the SOC may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, explained to the patient, and documented through informed consent for quality patient care and legal protection. This documentation is also valuable for the accumulation of new data, which can be retrospectively examined to allow for health care—and the SOC—to evolve.

The SOC articulate standards of care but also acknowledge the role of making informed choices and the value of harm-reduction approaches. In addition, this version of the SOC recognizes and validates various expressions of gender that may not necessitate psychological, hormonal, or surgical treatments. Some patients who present for care will have made significant self-directed progress towards gender role changes, transition, or other resolutions regarding their gender identity or gender dysphoria. Other patients will require more intensive services. Health professionals can use the SOC to help patients consider the full range of health services open to them, in accordance with their clinical needs and goals for gender expression.



Global Applicability of the *Standards of Care*

While the SOC are intended for worldwide use, WPATH acknowledges that much of the recorded clinical experience and knowledge in this area of health care is derived from North American and Western European sources. From place to place, both across and within nations, there are differences in all of the following: social attitudes towards transsexual, transgender, and gender-nonconforming people; constructions of gender roles and identities; language used to describe different gender identities; epidemiology of gender dysphoria; access to and cost of treatment; therapies offered; number and type of professionals who provide care; and legal and policy issues related to this area of health care (Winter, 2009).

It is impossible for the SOC to reflect all of these differences. In applying these standards to other cultural contexts, health professionals must be sensitive to these differences and adapt the SOC according to local realities. For example, in a number of cultures, gender-nonconforming people are found in such numbers and living in such ways as to make them highly socially visible (Peletz, 2006). In settings such as these, it is common for people to initiate a change in their gender expression and physical characteristics while in their teens or even earlier. Many grow up and live in a social, cultural, and even linguistic context quite unlike that of Western cultures. Yet almost all experience prejudice (Peletz, 2006; Winter, 2009). In many cultures, social stigma towards gender nonconformity is widespread and gender roles are highly prescriptive (Winter et al., 2009). Gender-nonconforming people in these settings are forced to be hidden and, therefore, may lack opportunities for adequate health care (Winter, 2009).

The SOC are not intended to limit efforts to provide the best available care to all individuals. Health professionals throughout the world—even in areas with limited resources and training opportunities—can apply the many core principles that undergird the SOC. These principles include the following: Exhibit respect for patients with nonconforming gender identities (do not pathologize differences in gender identity or expression); provide care (or refer to knowledgeable colleagues) that affirms patients' gender identities and reduces the distress of gender dysphoria, when present; become knowledgeable about the health care needs of transsexual, transgender, and gender-nonconforming people, including the benefits and risks of treatment options for gender dysphoria; match the treatment approach to the specific needs of patients, particularly their goals for gender expression and need for relief from gender dysphoria; facilitate access to appropriate care; seek patients' informed consent before providing treatment; offer continuity of care; and be prepared to support and advocate for patients within their families and communities (schools, workplaces, and other settings).

Terminology is culture- and time-dependent and is rapidly evolving. It is important to use respectful language in different places and times, and among different people. As the SOC are translated into other languages, great care must be taken to ensure that the meanings of terms are accurately translated. Terminology in English may not be easily translated into other languages, and vice versa. Some languages do not have equivalent words to describe the various terms within this document; hence, translators should be cognizant of the underlying goals of treatment and articulate culturally applicable guidance for reaching those goals.



The Difference Between Gender Nonconformity and Gender Dysphoria

Being Transsexual, Transgender, or Gender-Nonconforming Is a Matter of Diversity, Not Pathology

WPATH released a statement in May 2010 urging the de-psychopathologization of gender nonconformity worldwide (WPATH Board of Directors, 2010). This statement noted that “the expression of gender characteristics, including identities, that are not stereotypically associated with one’s assigned sex at birth is a common and culturally diverse human phenomenon [that] should not be judged as inherently pathological or negative.”

Unfortunately, there is stigma attached to gender nonconformity in many societies around the world. Such stigma can lead to prejudice and discrimination, resulting in “minority stress” (I. H. Meyer, 2003). Minority stress is unique (additive to general stressors experienced by all people), socially based, and chronic, and may make transsexual, transgender, and gender-nonconforming individuals more vulnerable to developing mental health concerns such as anxiety and depression (Institute of Medicine, 2011). In addition to prejudice and discrimination in society at large, stigma can contribute to abuse and neglect in one’s relationships with peers and family members, which in turn can lead to psychological distress. However, these symptoms are socially induced and are not inherent to being transsexual, transgender, or gender-nonconforming.

Gender Nonconformity Is Not the Same as Gender Dysphoria

Gender nonconformity refers to the extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex (Institute of Medicine, 2011). *Gender dysphoria* refers to discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b). Only *some* gender-nonconforming people experience gender dysphoria at *some* point in their lives.

Treatment is available to assist people with such distress to explore their gender identity and find a gender role that is comfortable for them (Bockting & Goldberg, 2006). Treatment is individualized: What helps one person alleviate gender dysphoria might be very different from what helps another person. This process may or may not involve a change in gender expression or body modifications. Medical treatment options include, for example, feminization or masculinization of the body through hormone therapy and/or surgery, which are effective in alleviating gender dysphoria and are medically necessary for many people. Gender identities and expressions are diverse, and hormones and surgery are just two of many options available to assist people with achieving comfort with self and identity.

Gender dysphoria can in large part be alleviated through treatment (Murad et al., 2010). Hence, while transsexual, transgender, and gender-nonconforming people may experience gender dysphoria at some points in their lives, many individuals who receive treatment will find a gender role and expression that is comfortable for them, even if these differ from those associated with their sex assigned at birth, or from prevailing gender norms and expectations.

Diagnoses Related to Gender Dysphoria

Some people experience gender dysphoria at such a level that the distress meets criteria for a formal diagnosis that might be classified as a mental disorder. Such a diagnosis is not a license for stigmatization or for the deprivation of civil and human rights. Existing classification systems such as the *Diagnostic Statistical Manual of Mental Disorders (DSM)* (American Psychiatric Association, 2000) and the *International Classification of Diseases (ICD)* (World Health Organization, 2007) define hundreds of mental disorders that vary in onset, duration, pathogenesis, functional disability, and treatability. All of these systems attempt to classify clusters of symptoms and conditions, not the individuals themselves. A disorder is a description of something with which a person might struggle, not a description of the person or the person's identity.

Thus, transsexual, transgender, and gender-nonconforming individuals are not inherently disordered. Rather, the distress of gender dysphoria, when present, is the concern that might be diagnosable and for which various treatment options are available. The existence of a diagnosis for such dysphoria often facilitates access to health care and can guide further research into effective treatments.

Research is leading to new diagnostic nomenclatures, and terms are changing in both the *DSM* (Cohen-Kettenis & Pfäfflin, 2010; Knudson, De Cuypere, & Bockting, 2010b; Meyer-Bahlburg, 2010; Zucker, 2010) and the *ICD*. For this reason, familiar terms are employed in the *SOC* and definitions are provided for terms that may be emerging. Health professionals should refer to the most current diagnostic criteria and appropriate codes to apply in their practice areas.

IV

Epidemiologic Considerations

Formal epidemiologic studies on the incidence^{III} and prevalence^{IV} of transsexualism specifically or transgender and gender-nonconforming identities in general have not been conducted, and efforts to achieve realistic estimates are fraught with enormous difficulties (Institute of Medicine, 2011; Zucker & Lawrence, 2009). Even if epidemiologic studies established that a similar proportion of transsexual, transgender, or gender-nonconforming people existed all over the world, it is likely that cultural differences from one country to another would alter both the behavioral expressions of different gender identities and the extent to which gender dysphoria—distinct from one's gender identity—is actually occurring in a population. While in most countries, crossing normative gender boundaries generates moral censure rather than compassion, there are examples in certain cultures of gender-nonconforming behaviors (e.g., in spiritual leaders) that are less stigmatized and even revered (Besnier, 1994; Bolin, 1988; Chiñas, 1995; Coleman, Colgan, & Gooren, 1992; Costa & Matzner, 2007; Jackson & Sullivan, 1999; Nanda, 1998; Taywaditap, Coleman, & Dumronggittigule, 1997).

For various reasons, researchers who have studied incidence and prevalence have tended to focus on the most easily counted subgroup of gender-nonconforming individuals: transsexual individuals who experience gender dysphoria and who present for gender-transition-related care at specialist gender clinics (Zucker & Lawrence, 2009). Most studies have been conducted in European countries such as Sweden (Wålinder, 1968, 1971), the United Kingdom (Hoenig & Kenna, 1974),

III **incidence**—the number of new cases arising in a given period (e.g., a year)

IV **prevalence**—the number of individuals having a condition, divided by the number of people in the general population

the Netherlands (Bakker, Van Kesteren, Gooren, & Bezemer, 1993; Eklund, Gooren, & Bezemer, 1988; van Kesteren, Gooren, & Megens, 1996), Germany (Weitze & Osburg, 1996), and Belgium (De Cuypere et al., 2007). One was conducted in Singapore (Tsoi, 1988).

De Cuypere and colleagues (2007) reviewed such studies, as well as conducted their own. Together, those studies span 39 years. Leaving aside two outlier findings from Pauly in 1965 and Tsoi in 1988, ten studies involving eight countries remain. The prevalence figures reported in these ten studies range from 1:11,900 to 1:45,000 for male-to-female individuals (MtF) and 1:30,400 to 1:200,000 for female-to-male (FtM) individuals. Some scholars have suggested that the prevalence is much higher, depending on the methodology used in the research (e.g., Olyslager & Conway, 2007).

Direct comparisons across studies are impossible, as each differed in their data collection methods and in their criteria for documenting a person as transsexual (e.g., whether or not a person had undergone genital reconstruction, versus had initiated hormone therapy, versus had come to the clinic seeking medically supervised transition services). The trend appears to be towards higher prevalence rates in the more recent studies, possibly indicating increasing numbers of people seeking clinical care. Support for this interpretation comes from research by Reed and colleagues (2009), who reported a doubling of the numbers of people accessing care at gender clinics in the United Kingdom every five or six years. Similarly, Zucker and colleagues (2008) reported a four- to five-fold increase in child and adolescent referrals to their Toronto, Canada clinic over a 30-year period.

The numbers yielded by studies such as these can be considered minimum estimates at best. The published figures are mostly derived from clinics where patients met criteria for severe gender dysphoria and had access to health care at those clinics. These estimates do not take into account that treatments offered in a particular clinic setting might not be perceived as affordable, useful, or acceptable by all self-identified gender dysphoric individuals in a given area. By counting only those people who present at clinics for a specific type of treatment, an unspecified number of gender dysphoric individuals are overlooked.

Other clinical observations (not yet firmly supported by systematic study) support the likelihood of a higher prevalence of gender dysphoria: (i) Previously unrecognized gender dysphoria is occasionally diagnosed when patients are seen with anxiety, depression, conduct disorder, substance abuse, dissociative identity disorders, borderline personality disorder, sexual disorders, and disorders of sex development (Cole, O'Boyle, Emory, & Meyer III, 1997). (ii) Some crossdressers, drag queens/kings or female/male impersonators, and gay and lesbian individuals may be experiencing gender dysphoria (Bullough & Bullough, 1993). (iii) The intensity of some people's gender dysphoria fluctuates below and above a clinical threshold (Docter, 1988). (iv) Gender nonconformity among FtM individuals tends to be relatively invisible in many cultures, particularly to Western health

professionals and researchers who have conducted most of the studies on which the current estimates of prevalence and incidence are based (Winter, 2009).

Overall, the existing data should be considered a starting point, and health care would benefit from more rigorous epidemiologic study in different locations worldwide.



Overview of Therapeutic Approaches for Gender Dysphoria

Advancements in the Knowledge and Treatment of Gender Dysphoria

In the second half of the 20th century, awareness of the phenomenon of gender dysphoria increased when health professionals began to provide assistance to alleviate gender dysphoria by supporting changes in primary and secondary sex characteristics through hormone therapy and surgery, along with a change in gender role. Although Harry Benjamin already acknowledged a spectrum of gender nonconformity (Benjamin, 1966), the initial clinical approach largely focused on identifying who was an appropriate candidate for sex reassignment to facilitate a physical change from male to female or female to male as completely as possible (e.g., Green & Fleming, 1990; Hastings, 1974). This approach was extensively evaluated and proved to be highly effective. Satisfaction rates across studies ranged from 87% of MtF patients to 97% of FtM patients (Green & Fleming, 1990), and regrets were extremely rare (1–1.5% of MtF patients and <1% of FtM patients; Pfäfflin, 1993). Indeed, hormone therapy and surgery have been found to be medically necessary to alleviate gender dysphoria in many people (American Medical Association, 2008; Anton, 2009; World Professional Association for Transgender Health, 2008).

As the field matured, health professionals recognized that while many individuals need both hormone therapy and surgery to alleviate their gender dysphoria, others need only one of these treatment options and some need neither (Bockting & Goldberg, 2006; Bockting, 2008; Lev, 2004). Often with the help of psychotherapy, some individuals integrate their trans- or cross-gender feelings into the gender role they were assigned at birth and do not feel the need to feminize or masculinize their body. For others, changes in gender role and expression are sufficient to alleviate

gender dysphoria. Some patients may need hormones, a possible change in gender role, but not surgery; others may need a change in gender role along with surgery, but not hormones. In other words, treatment for gender dysphoria has become more individualized.

As a generation of transsexual, transgender, and gender-nonconforming individuals has come of age—many of whom have benefitted from different therapeutic approaches—they have become more visible as a community and demonstrated considerable diversity in their gender identities, roles, and expressions. Some individuals describe themselves not as gender-nonconforming but as unambiguously cross-sexed (i.e., as a member of the other sex; Bockting, 2008). Other individuals affirm their unique gender identity and no longer consider themselves to be either male or female (Bornstein, 1994; Kimberly, 1997; Stone, 1991; Warren, 1993). Instead, they may describe their gender identity in specific terms such as transgender, bigender, or genderqueer, affirming their unique experiences that may transcend a male/female binary understanding of gender (Bockting, 2008; Ekins & King, 2006; Nestle, Wilchins, & Howell, 2002). They may not experience their process of identity affirmation as a “transition,” because they never fully embraced the gender role they were assigned at birth or because they actualize their gender identity, role, and expression in a way that does not involve a change from one gender role to another. For example, some youth identifying as genderqueer have always experienced their gender identity and role as such (genderqueer). Greater public visibility and awareness of gender diversity (Feinberg, 1996) has further expanded options for people with gender dysphoria to actualize an identity and find a gender role and expression that are comfortable for them.

Health professionals can assist gender dysphoric individuals with affirming their gender identity, exploring different options for expression of that identity, and making decisions about medical treatment options for alleviating gender dysphoria.

Options for Psychological and Medical Treatment of Gender Dysphoria

For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one’s gender identity);
- Hormone therapy to feminize or masculinize the body;

- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience.

Options for Social Support and Changes in Gender Expression

In addition (or as an alternative) to the psychological- and medical-treatment options described above, other options can be considered to help alleviate gender dysphoria, for example:

- In-person and online peer support resources, groups, or community organizations that provide avenues for social support and advocacy;
- In-person and online support resources for families and friends;
- Voice and communication therapy to help individuals develop verbal and non-verbal communication skills that facilitate comfort with their gender identity;
- Hair removal through electrolysis, laser treatment, or waxing;
- Breast binding or padding, genital tucking or penile prostheses, padding of hips or buttocks;
- Changes in name and gender marker on identity documents.

VI

Assessment and Treatment of Children and Adolescents With Gender Dysphoria

There are a number of differences in the phenomenology, developmental course, and treatment approaches for gender dysphoria in children, adolescents, and adults. In children and adolescents, a rapid and dramatic developmental process (physical, psychological, and sexual) is involved and

there is greater fluidity and variability in outcomes, particularly in prepubertal children. Accordingly, this section of the SOC offers specific clinical guidelines for the assessment and treatment of gender dysphoric children and adolescents.

Differences Between Children and Adolescents with Gender Dysphoria

An important difference between gender dysphoric children and adolescents is in the proportion for whom dysphoria persists into adulthood. Gender dysphoria during childhood does not inevitably continue into adulthood.^V Rather, in follow-up studies of prepubertal children (mainly boys) who were referred to clinics for assessment of gender dysphoria, the dysphoria persisted into adulthood for only 6–23% of children (Cohen-Kettenis, 2001; Zucker & Bradley, 1995). Boys in these studies were more likely to identify as gay in adulthood than as transgender (Green, 1987; Money & Russo, 1979; Zucker & Bradley, 1995; Zuger, 1984). Newer studies, also including girls, showed a 12–27% persistence rate of gender dysphoria into adulthood (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Wallien & Cohen-Kettenis, 2008).

In contrast, the persistence of gender dysphoria into adulthood appears to be much higher for adolescents. No formal prospective studies exist. However, in a follow-up study of 70 adolescents who were diagnosed with gender dysphoria and given puberty-suppressing hormones, all continued with actual sex reassignment, beginning with feminizing/masculinizing hormone therapy (de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2010).

Another difference between gender dysphoric children and adolescents is in the sex ratios for each age group. In clinically referred, gender dysphoric children under age 12, the male/female ratio ranges from 6:1 to 3:1 (Zucker, 2004). In clinically referred, gender dysphoric adolescents older than age 12, the male/female ratio is close to 1:1 (Cohen-Kettenis & Pfäfflin, 2003).

As discussed in section IV and by Zucker and Lawrence (2009), formal epidemiologic studies on gender dysphoria—in children, adolescents, and adults—are lacking. Additional research is needed to refine estimates of its prevalence and persistence in different populations worldwide.

^V Gender-nonconforming behaviors in children may continue into adulthood, but such behaviors are not necessarily indicative of gender dysphoria and a need for treatment. As described in section III, gender dysphoria is not synonymous with diversity in gender expression.

Phenomenology in Children

Children as young as age two may show features that could indicate gender dysphoria. They may express a wish to be of the other sex and be unhappy about their physical sex characteristics and functions. In addition, they may prefer clothes, toys, and games that are commonly associated with the other sex and prefer playing with other-sex peers. There appears to be heterogeneity in these features: Some children demonstrate extremely gender-nonconforming behavior and wishes, accompanied by persistent and severe discomfort with their primary sex characteristics. In other children, these characteristics are less intense or only partially present (Cohen-Kettenis et al., 2006; Knudson, De Cuypere, & Bockting, 2010a).

It is relatively common for gender dysphoric children to have coexisting internalizing disorders such as anxiety and depression (Cohen-Kettenis, Owen, Kaijser, Bradley, & Zucker, 2003; Wallien, Swaab, & Cohen-Kettenis, 2007; Zucker, Owen, Bradley, & Ameeriar, 2002). The prevalence of autism spectrum disorders seems to be higher in clinically referred, gender dysphoric children than in the general population (de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010).

Phenomenology in Adolescents

In most children, gender dysphoria will disappear before, or early in, puberty. However, in some children these feelings will intensify and body aversion will develop or increase as they become adolescents and their secondary sex characteristics develop (Cohen-Kettenis, 2001; Cohen-Kettenis & Pfäfflin, 2003; Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008; Zucker & Bradley, 1995). Data from one study suggest that more extreme gender nonconformity in childhood is associated with persistence of gender dysphoria into late adolescence and early adulthood (Wallien & Cohen-Kettenis, 2008). Yet many adolescents and adults presenting with gender dysphoria do not report a history of childhood gender-nonconforming behaviors (Dokter, 1988; Landén, Wälinder, & Lundström, 1998). Therefore, it may come as a surprise to others (parents, other family members, friends, and community members) when a youth's gender dysphoria first becomes evident in adolescence.

Adolescents who experience their primary and/or secondary sex characteristics and their sex assigned at birth as inconsistent with their gender identity may be intensely distressed about it. Many, but not all, gender dysphoric adolescents have a strong wish for hormones and surgery. Increasing numbers of adolescents have already started living in their desired gender role upon entering high school (Cohen-Kettenis & Pfäfflin, 2003).

Among adolescents who are referred to gender identity clinics, the number considered eligible for early medical treatment—starting with GnRH analogues to suppress puberty in the first Tanner stages—differs among countries and centers. Not all clinics offer puberty suppression. If such treatment is offered, the pubertal stage at which adolescents are allowed to start varies from Tanner stage 2 to stage 4 (Delemarre-van de Waal & Cohen-Kettenis, 2006; Zucker et al., 2012). The percentages of treated adolescents are likely influenced by the organization of health care, insurance aspects, cultural differences, opinions of health professionals, and diagnostic procedures offered in different settings.

Inexperienced clinicians may mistake indications of gender dysphoria for delusions. Phenomenologically, there is a qualitative difference between the presentation of gender dysphoria and the presentation of delusions or other psychotic symptoms. The vast majority of children and adolescents with gender dysphoria are not suffering from underlying severe psychiatric illness such as psychotic disorders (Steensma, Biemond, de Boer, & Cohen-Kettenis, published online ahead of print January 7, 2011).

It is more common for adolescents with gender dysphoria to have coexisting internalizing disorders such as anxiety and depression, and/or externalizing disorders such as oppositional defiant disorder (de Vries et al., 2010). As in children, there seems to be a higher prevalence of autistic spectrum disorders in clinically referred, gender dysphoric adolescents than in the general adolescent population (de Vries et al., 2010).

Competency of Mental Health Professionals Working with Children or Adolescents with Gender Dysphoria

The following are recommended minimum credentials for mental health professionals who assess, refer, and offer therapy to children and adolescents presenting with gender dysphoria:

1. Meet the competency requirements for mental health professionals working with adults, as outlined in section VII;
2. Trained in childhood and adolescent developmental psychopathology;
3. Competent in diagnosing and treating the ordinary problems of children and adolescents.

Roles of Mental Health Professionals Working with Children and Adolescents with Gender Dysphoria

The roles of mental health professionals working with gender dysphoric children and adolescents may include the following:

1. Directly assess gender dysphoria in children and adolescents (see general guidelines for assessment, below).
2. Provide family counseling and supportive psychotherapy to assist children and adolescents with exploring their gender identity, alleviating distress related to their gender dysphoria, and ameliorating any other psychosocial difficulties.
3. Assess and treat any coexisting mental health concerns of children or adolescents (or refer to another mental health professional for treatment). Such concerns should be addressed as part of the overall treatment plan.
4. Refer adolescents for additional physical interventions (such as puberty-suppressing hormones) to alleviate gender dysphoria. The referral should include documentation of an assessment of gender dysphoria and mental health, the adolescent's eligibility for physical interventions (outlined below), the mental health professional's relevant expertise, and any other information pertinent to the youth's health and referral for specific treatments.
5. Educate and advocate on behalf of gender dysphoric children, adolescents, and their families in their community (e.g., day care centers, schools, camps, other organizations). This is particularly important in light of evidence that children and adolescents who do not conform to socially prescribed gender norms may experience harassment in school (Grossman, D'Augelli, & Salter, 2006; Grossman, D'Augelli, Howell, & Hubbard, 2006; Sausa, 2005), putting them at risk for social isolation, depression, and other negative sequelae (Nuttbrock et al., 2010).
6. Provide children, youth, and their families with information and referral for peer support, such as support groups for parents of gender-nonconforming and transgender children (Gold & MacNish, 2011; Pleak, 1999; Rosenberg, 2002).

Assessment and psychosocial interventions for children and adolescents are often provided within a multidisciplinary gender identity specialty service. If such a multidisciplinary service is not available, a mental health professional should provide consultation and liaison arrangements with a pediatric endocrinologist for the purpose of assessment, education, and involvement in any decisions about physical interventions.

Psychological Assessment of Children and Adolescents

When assessing children and adolescents who present with gender dysphoria, mental health professionals should broadly conform to the following guidelines:

1. Mental health professionals should not dismiss or express a negative attitude towards nonconforming gender identities or indications of gender dysphoria. Rather, they should acknowledge the presenting concerns of children, adolescents, and their families; offer a thorough assessment for gender dysphoria and any coexisting mental health concerns; and educate clients and their families about therapeutic options, if needed. Acceptance, and alleviation of secrecy, can bring considerable relief to gender dysphoric children/adolescents and their families.
2. Assessment of gender dysphoria and mental health should explore the nature and characteristics of a child's or adolescent's gender identity. A psychodiagnostic and psychiatric assessment—covering the areas of emotional functioning, peer and other social relationships, and intellectual functioning/school achievement—should be performed. Assessment should include an evaluation of the strengths and weaknesses of family functioning. Emotional and behavioral problems are relatively common, and unresolved issues in a child's or youth's environment may be present (de Vries, Doreleijers, Steensma, & Cohen-Kettenis, 2011; Di Ceglie & Thümmel, 2006; Wallien et al., 2007).
3. For adolescents, the assessment phase should also be used to inform youth and their families about the possibilities and limitations of different treatments. This is necessary for informed consent, but also important for assessment. The way that adolescents respond to information about the reality of sex reassignment can be diagnostically informative. Correct information may alter a youth's desire for certain treatment, if the desire was based on unrealistic expectations of its possibilities.

Psychological and Social Interventions for Children and Adolescents

When supporting and treating children and adolescents with gender dysphoria, health professionals should broadly conform to the following guidelines:

1. Mental health professionals should help families to have an accepting and nurturing response to the concerns of their gender dysphoric child or adolescent. Families play an important role in the psychological health and well-being of youth (Brill & Pepper, 2008; Lev, 2004). This also applies to peers and mentors from the community, who can be another source of social support.

2. Psychotherapy should focus on reducing a child's or adolescent's distress related to the gender dysphoria and on ameliorating any other psychosocial difficulties. For youth pursuing sex reassignment, psychotherapy may focus on supporting them before, during, and after reassignment. Formal evaluations of different psychotherapeutic approaches for this situation have not been published, but several counseling methods have been described (Cohen-Kettenis, 2006; de Vries, Cohen-Kettenis, & Delemarre-van de Waal, 2006; Di Ceglie & Thümmel, 2006; Hill, Menvielle, Sica, & Johnson, 2010; Malpas, in press; Menvielle & Tuerk, 2002; Rosenberg, 2002; Vanderburgh, 2009; Zucker, 2006).

Treatment aimed at trying to change a person's gender identity and expression to become more congruent with sex assigned at birth has been attempted in the past without success (Gelder & Marks, 1969; Greenson, 1964), particularly in the long term (Cohen-Kettenis & Kuiper, 1984; Pauly, 1965). Such treatment is no longer considered ethical.

3. Families should be supported in managing uncertainty and anxiety about their child's or adolescent's psychosexual outcomes and in helping youth to develop a positive self-concept.
4. Mental health professionals should not impose a binary view of gender. They should give ample room for clients to explore different options for gender expression. Hormonal or surgical interventions are appropriate for some adolescents, but not for others.
5. Clients and their families should be supported in making difficult decisions regarding the extent to which clients are allowed to express a gender role that is consistent with their gender identity, as well as the timing of changes in gender role and possible social transition. For example, a client might attend school while undergoing social transition only partly (e.g., by wearing clothing and having a hairstyle that reflects gender identity) or completely (e.g., by also using a name and pronouns congruent with gender identity). Difficult issues include whether and when to inform other people of the client's situation, and how others in their lives might respond.
6. Health professionals should support clients and their families as educators and advocates in their interactions with community members and authorities such as teachers, school boards, and courts.
7. Mental health professionals should strive to maintain a therapeutic relationship with gender-nonconforming children/adolescents and their families throughout any subsequent social changes or physical interventions. This ensures that decisions about gender expression and the treatment of gender dysphoria are thoughtfully and recurrently considered. The same reasoning applies if a child or adolescent has already socially changed gender role prior to being seen by a mental health professional.

Social Transition in Early Childhood

Some children state that they want to make a social transition to a different gender role long before puberty. For some children, this may reflect an expression of their gender identity. For others, this could be motivated by other forces. Families vary in the extent to which they allow their young children to make a social transition to another gender role. Social transitions in early childhood do occur within some families with early success. This is a controversial issue, and divergent views are held by health professionals. The current evidence base is insufficient to predict the long-term outcomes of completing a gender role transition during early childhood. Outcomes research with children who completed early social transitions would greatly inform future clinical recommendations.

Mental health professionals can help families to make decisions regarding the timing and process of any gender role changes for their young children. They should provide information and help parents to weigh the potential benefits and challenges of particular choices. Relevant in this respect are the previously described relatively low persistence rates of childhood gender dysphoria (Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008). A change back to the original gender role can be highly distressing and even result in postponement of this second social transition on the child's part (Steensma & Cohen-Kettenis, 2011). For reasons such as these, parents may want to present this role change as an exploration of living in another gender role rather than an irreversible situation. Mental health professionals can assist parents in identifying potential in-between solutions or compromises (e.g., only when on vacation). It is also important that parents explicitly let the child know that there is a way back.

Regardless of a family's decisions regarding transition (timing, extent), professionals should counsel and support them as they work through the options and implications. If parents do not allow their young child to make a gender-role transition, they may need counseling to assist them with meeting their child's needs in a sensitive and nurturing way, ensuring that the child has ample possibilities to explore gender feelings and behavior in a safe environment. If parents do allow their young child to make a gender role transition, they may need counseling to facilitate a positive experience for their child. For example, they may need support in using correct pronouns, maintaining a safe and supportive environment for their transitioning child (e.g., in school, peer group settings), and communicating with other people in their child's life. In either case, as a child nears puberty, further assessment may be needed as options for physical interventions become relevant.

Physical Interventions for Adolescents

Before any physical interventions are considered for adolescents, extensive exploration of psychological, family, and social issues should be undertaken, as outlined above. The duration of this exploration may vary considerably depending on the complexity of the situation.

Physical interventions should be addressed in the context of adolescent development. Some identity beliefs in adolescents may become firmly held and strongly expressed, giving a false impression of irreversibility. An adolescent's shift towards gender conformity can occur primarily to please the parents and may not persist or reflect a permanent change in gender dysphoria (Hembree et al., 2009; Steensma et al., published online ahead of print January 7, 2011).

Physical interventions for adolescents fall into three categories or stages (Hembree et al., 2009):

1. *Fully reversible interventions.* These involve the use of GnRH analogues to suppress estrogen or testosterone production and consequently delay the physical changes of puberty. Alternative treatment options include progestins (most commonly medroxyprogesterone) or other medications (such as spironolactone) that decrease the effects of androgens secreted by the testicles of adolescents who are not receiving GnRH analogues. Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses.
2. *Partially reversible interventions.* These include hormone therapy to masculinize or feminize the body. Some hormone-induced changes may need reconstructive surgery to reverse the effect (e.g., gynaecomastia caused by estrogens), while other changes are not reversible (e.g., deepening of the voice caused by testosterone).
3. *Irreversible interventions.* These are surgical procedures.

A staged process is recommended to keep options open through the first two stages. Moving from one stage to another should not occur until there has been adequate time for adolescents and their parents to assimilate fully the effects of earlier interventions.

Fully Reversible Interventions

Adolescents may be eligible for puberty-suppressing hormones as soon as pubertal changes have begun. In order for adolescents and their parents to make an informed decision about pubertal delay, it is recommended that adolescents experience the onset of puberty to at least Tanner Stage 2. Some children may arrive at this stage at very young ages (e.g., 9 years of age). Studies

evaluating this approach have only included children who were at least 12 years of age (Cohen-Kettenis, Schagen, Steensma, de Vries, & Delemarre-van de Waal, 2011; de Vries, Steensma et al., 2010; Delemarre-van de Waal, van Weissenbruch, & Cohen Kettenis, 2004; Delemarre-van de Waal & Cohen-Kettenis, 2006).

Two goals justify intervention with puberty-suppressing hormones: (i) their use gives adolescents more time to explore their gender nonconformity and other developmental issues; and (ii) their use may facilitate transition by preventing the development of sex characteristics that are difficult or impossible to reverse if adolescents continue on to pursue sex reassignment.

Puberty suppression may continue for a few years, at which time a decision is made to either discontinue all hormone therapy or transition to a feminizing/masculinizing hormone regimen. Pubertal suppression does not inevitably lead to social transition or to sex reassignment.

Criteria for Puberty-Suppressing Hormones

In order for adolescents to receive puberty-suppressing hormones, the following minimum criteria must be met:

1. The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);
2. Gender dysphoria emerged or worsened with the onset of puberty;
3. Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment;
4. The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

Regimens, Monitoring, and Risks for Puberty Suppression

For puberty suppression, adolescents with male genitalia should be treated with GnRH analogues, which stop luteinizing hormone secretion and therefore testosterone secretion. Alternatively, they may be treated with progestins (such as medroxyprogesterone) or with other medications that block testosterone secretion and/or neutralize testosterone action. Adolescents with female genitalia should be treated with GnRH analogues, which stop the production of estrogens and

progesterone. Alternatively, they may be treated with progestins (such as medroxyprogesterone). Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses. In both groups of adolescents, use of GnRH analogues is the preferred treatment (Hembree et al., 2009), but their high cost is prohibitive for some patients.

During pubertal suppression, an adolescent's physical development should be carefully monitored—preferably by a pediatric endocrinologist—so that any necessary interventions can occur (e.g., to establish an adequate gender appropriate height, to improve iatrogenic low bone mineral density) (Hembree et al., 2009).

Early use of puberty-suppressing hormones may avert negative social and emotional consequences of gender dysphoria more effectively than their later use would. Intervention in early adolescence should be managed with pediatric endocrinological advice, when available. Adolescents with male genitalia who start GnRH analogues early in puberty should be informed that this could result in insufficient penile tissue for penile inversion vaginoplasty techniques (alternative techniques, such as the use of a skin graft or colon tissue, are available).

Neither puberty suppression nor allowing puberty to occur is a neutral act. On the one hand, functioning in later life can be compromised by the development of irreversible secondary sex characteristics during puberty and by years spent experiencing intense gender dysphoria. On the other hand, there are concerns about negative physical side effects of GnRH analogue use (e.g., on bone development and height). Although the very first results of this approach (as assessed for adolescents followed over 10 years) are promising (Cohen-Kettenis et al., 2011; Delemarre-van de Waal & Cohen-Kettenis, 2006), the long-term effects can only be determined when the earliest-treated patients reach the appropriate age.

Partially Reversible Interventions

Adolescents may be eligible to begin feminizing/masculinizing hormone therapy, preferably with parental consent. In many countries, 16-year-olds are legal adults for medical decision-making and do not require parental consent. Ideally, treatment decisions should be made among the adolescent, the family, and the treatment team.

Regimens for hormone therapy in gender dysphoric adolescents differ substantially from those used in adults (Hembree et al., 2009). The hormone regimens for youth are adapted to account for the somatic, emotional, and mental development that occurs throughout adolescence (Hembree et al., 2009).

Irreversible Interventions

Genital surgery should not be carried out until (i) patients reach the legal age of majority to give consent for medical procedures in a given country, and (ii) patients have lived continuously for at least 12 months in the gender role that is congruent with their gender identity. The age threshold should be seen as a minimum criterion and not an indication in and of itself for active intervention.

Chest surgery in FtM patients could be carried out earlier, preferably after ample time of living in the desired gender role and after one year of testosterone treatment. The intent of this suggested sequence is to give adolescents sufficient opportunity to experience and socially adjust in a more masculine gender role, before undergoing irreversible surgery. However, different approaches may be more suitable, depending on an adolescent's specific clinical situation and goals for gender identity expression.

Risks of Withholding Medical Treatment for Adolescents

Refusing timely medical interventions for adolescents might prolong gender dysphoria and contribute to an appearance that could provoke abuse and stigmatization. As the level of gender-related abuse is strongly associated with the degree of psychiatric distress during adolescence (Nuttbrock et al., 2010), withholding puberty suppression and subsequent feminizing or masculinizing hormone therapy is not a neutral option for adolescents.

VII

Mental Health

Transsexual, transgender, and gender-nonconforming people might seek the assistance of a mental health professional for any number of reasons. Regardless of a person's reason for seeking care, mental health professionals should have familiarity with gender nonconformity, act with appropriate cultural competence, and exhibit sensitivity in providing care.

This section of the SOC focuses on the role of mental health professionals in the care of adults seeking help for gender dysphoria and related concerns. Professionals working with gender dysphoric children, adolescents, and their families should consult section VI.

Competency of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria

The training of mental health professionals competent to work with gender dysphoric adults rests upon basic general clinical competence in the assessment, diagnosis, and treatment of mental health concerns. Clinical training may occur within any discipline that prepares mental health professionals for clinical practice, such as psychology, psychiatry, social work, mental health counseling, marriage and family therapy, nursing, or family medicine with specific training in behavioral health and counseling. The following are recommended minimum credentials for mental health professionals who work with adults presenting with gender dysphoria:

1. A master's degree or its equivalent in a clinical behavioral science field. This degree, or a more advanced one, should be granted by an institution accredited by the appropriate national or regional accrediting board. The mental health professional should have documented credentials from a relevant licensing board or equivalent for that country.
2. Competence in using the *Diagnostic Statistical Manual of Mental Disorders* and/or the *International Classification of Diseases* for diagnostic purposes.
3. Ability to recognize and diagnose coexisting mental health concerns and to distinguish these from gender dysphoria.
4. Documented supervised training and competence in psychotherapy or counseling.
5. Knowledgeable about gender-nonconforming identities and expressions, and the assessment and treatment of gender dysphoria.
6. Continuing education in the assessment and treatment of gender dysphoria. This may include attending relevant professional meetings, workshops, or seminars; obtaining supervision from a mental health professional with relevant experience; or participating in research related to gender nonconformity and gender dysphoria.

In addition to the minimum credentials above, it is recommended that mental health professionals develop and maintain cultural competence to facilitate their work with transsexual, transgender, and gender-nonconforming clients. This may involve, for example, becoming knowledgeable about current community, advocacy, and public policy issues relevant to these clients and their families. Additionally, knowledge about sexuality, sexual health concerns, and the assessment and treatment of sexual disorders is preferred.

Mental health professionals who are new to the field (irrespective of their level of training and other experience) should work under the supervision of a mental health professional with established competence in the assessment and treatment of gender dysphoria.

Tasks of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria

Mental health professionals may serve transsexual, transgender, and gender-nonconforming individuals and their families in many ways, depending on a client's needs. For example, mental health professionals may serve as a psychotherapist, counselor, or family therapist, or as a diagnostician/assessor, advocate, or educator.

Mental health professionals should determine a client's reasons for seeking professional assistance. For example, a client may be presenting for any combination of the following health care services: psychotherapeutic assistance to explore gender identity and expression or to facilitate a coming-out process; assessment and referral for feminizing/masculinizing medical interventions; psychological support for family members (partners, children, extended family); psychotherapy unrelated to gender concerns; or other professional services.

Below are general guidelines for common tasks that mental health professionals may fulfill in working with adults who present with gender dysphoria.

Tasks Related to Assessment and Referral

1. Assess Gender Dysphoria

Mental health professionals assess clients' gender dysphoria in the context of an evaluation of their psychosocial adjustment (Bockting et al., 2006; Lev, 2004, 2009). The evaluation includes, at a minimum, assessment of gender identity and gender dysphoria, history and development of gender dysphoric feelings, the impact of stigma attached to gender nonconformity on mental health, and the availability of support from family, friends, and peers (for example, in-person or online contact with other transsexual, transgender, or gender-nonconforming individuals or groups). The evaluation may result in no diagnosis, in a formal diagnosis related to gender dysphoria, and/or in other diagnoses that describe aspects of the client's health and psychosocial adjustment. The role

of mental health professionals includes making reasonably sure that the gender dysphoria is not secondary to, or better accounted for, by other diagnoses.

Mental health professionals with the competencies described above (hereafter called “a qualified mental health professional”) are best prepared to conduct this assessment of gender dysphoria. However, this task may instead be conducted by another type of health professional who has appropriate training in behavioral health and is competent in the assessment of gender dysphoria, particularly when functioning as part of a multidisciplinary specialty team that provides access to feminizing/masculinizing hormone therapy. This professional may be the prescribing hormone therapy provider or a member of that provider’s health care team.

2. Provide Information Regarding Options for Gender Identity and Expression and Possible Medical Interventions

An important task of mental health professionals is to educate clients regarding the diversity of gender identities and expressions and the various options available to alleviate gender dysphoria. Mental health professionals then may facilitate a process (or refer elsewhere) in which clients explore these various options, with the goals of finding a comfortable gender role and expression and becoming prepared to make a fully informed decision about available medical interventions, if needed. This process may include referral for individual, family, and group therapy and/or to community resources and avenues for peer support. The professional and the client discuss the implications, both short- and long-term, of any changes in gender role and use of medical interventions. These implications can be psychological, social, physical, sexual, occupational, financial, and legal (Bockting et al., 2006; Lev, 2004).

This task is also best conducted by a qualified mental health professional, but may be conducted by another health professional with appropriate training in behavioral health and with sufficient knowledge about gender-nonconforming identities and expressions and about possible medical interventions for gender dysphoria, particularly when functioning as part of a multidisciplinary specialty team that provides access to feminizing/masculinizing hormone therapy.

3. Assess, Diagnose, and Discuss Treatment Options for Coexisting Mental Health Concerns

Clients presenting with gender dysphoria may struggle with a range of mental health concerns (Gómez-Gil, Trilla, Salamero, Godás, & Valdés, 2009; Murad et al., 2010) whether related or unrelated to what is often a long history of gender dysphoria and/or chronic minority stress. Possible concerns include anxiety, depression, self-harm, a history of abuse and neglect, compulsivity, substance abuse, sexual concerns, personality disorders, eating disorders, psychotic disorders, and autistic spectrum disorders (Bockting et al., 2006; Nuttbrock et al., 2010; Robinow, 2009). Mental health professionals should screen for these and other mental health concerns and incorporate

the identified concerns into the overall treatment plan. These concerns can be significant sources of distress and, if left untreated, can complicate the process of gender identity exploration and resolution of gender dysphoria (Bockting et al., 2006; Fraser, 2009a; Lev, 2009). Addressing these concerns can greatly facilitate the resolution of gender dysphoria, possible changes in gender role, the making of informed decisions about medical interventions, and improvements in quality of life.

Some clients may benefit from psychotropic medications to alleviate symptoms or treat coexisting mental health concerns. Mental health professionals are expected to recognize this and either provide pharmacotherapy or refer to a colleague who is qualified to do so. The presence of coexisting mental health concerns does not necessarily preclude possible changes in gender role or access to feminizing/masculinizing hormones or surgery; rather, these concerns need to be optimally managed prior to, or concurrent with, treatment of gender dysphoria. In addition, clients should be assessed for their ability to provide educated and informed consent for medical treatments.

Qualified mental health professionals are specifically trained to assess, diagnose, and treat (or refer to treatment for) these coexisting mental health concerns. Other health professionals with appropriate training in behavioral health, particularly when functioning as part of a multidisciplinary specialty team providing access to feminizing/masculinizing hormone therapy, may also screen for mental health concerns and, if indicated, provide referral for comprehensive assessment and treatment by a qualified mental health professional.

4. If Applicable, Assess Eligibility, Prepare, and Refer for Hormone Therapy

The SOC provide criteria to guide decisions regarding feminizing/masculinizing hormone therapy (outlined in section VIII and Appendix C). Mental health professionals can help clients who are considering hormone therapy to be both psychologically prepared (e.g., client has made a fully informed decision with clear and realistic expectations; is ready to receive the service in line with the overall treatment plan; has included family and community as appropriate) and practically prepared (e.g., has been evaluated by a physician to rule out or address medical contraindications to hormone use; has considered the psychosocial implications). If clients are of childbearing age, reproductive options (section IX) should be explored before initiating hormone therapy.

It is important for mental health professionals to recognize that decisions about hormones are first and foremost a client's decisions—as are all decisions regarding healthcare. However, mental health professionals have a responsibility to encourage, guide, and assist clients with making fully informed decisions and becoming adequately prepared. To best support their clients' decisions, mental health professionals need to have functioning working relationships with their clients and sufficient information about them. Clients should receive prompt and attentive evaluation, with the goal of alleviating their gender dysphoria and providing them with appropriate medical services.

Referral for feminizing/masculinizing hormone therapy

People may approach a specialized provider in any discipline to pursue feminizing/masculinizing hormone therapy. However, transgender health care is an interdisciplinary field, and coordination of care and referral among a client's overall care team is recommended.

Hormone therapy can be initiated with a referral from a qualified mental health professional. Alternatively, a health professional who is appropriately trained in behavioral health and competent in the assessment of gender dysphoria may assess eligibility, prepare, and refer the patient for hormone therapy, particularly in the absence of significant coexisting mental health concerns and when working in the context of a multidisciplinary specialty team. The referring health professional should provide documentation—in the chart and/or referral letter—of the patient's personal and treatment history, progress, and eligibility. Health professionals who recommend hormone therapy share the ethical and legal responsibility for that decision with the physician who provides the service.

The recommended content of the referral letter for feminizing/masculinizing hormone therapy is as follows:

1. The client's general identifying characteristics;
2. Results of the client's psychosocial assessment, including any diagnoses;
3. The duration of the referring health professional's relationship with the client, including the type of evaluation and therapy or counseling to date;
4. An explanation that the criteria for hormone therapy have been met, and a brief description of the clinical rationale for supporting the client's request for hormone therapy;
5. A statement that informed consent has been obtained from the patient;
6. A statement that the referring health professional is available for coordination of care and welcomes a phone call to establish this.

For providers working within a multidisciplinary specialty team, a letter may not be necessary; rather, the assessment and recommendation can be documented in the patient's chart.

5. If Applicable, Assess Eligibility, Prepare, and Refer for Surgery

The SOC also provide criteria to guide decisions regarding breast/chest surgery and genital surgery (outlined in section XI and Appendix C). Mental health professionals can help clients who are

considering surgery to be both psychologically prepared (e.g., has made a fully informed decision with clear and realistic expectations; is ready to receive the service in line with the overall treatment plan; has included family and community as appropriate) and practically prepared (e.g., has made an informed choice about a surgeon to perform the procedure; has arranged aftercare). If clients are of childbearing age, reproductive options (section IX) should be explored before undergoing genital surgery.

The SOC do not state criteria for other surgical procedures, such as feminizing or masculinizing facial surgery; however, mental health professionals can play an important role in helping their clients to make fully informed decisions about the timing and implications of such procedures in the context of the overall coming-out or transition process.

It is important for mental health professionals to recognize that decisions about surgery are first and foremost a client's decisions—as are all decisions regarding healthcare. However, mental health professionals have a responsibility to encourage, guide, and assist clients with making fully informed decisions and becoming adequately prepared. To best support their clients' decisions, mental health professionals need to have functioning working relationships with their clients and sufficient information about them. Clients should receive prompt and attentive evaluation, with the goal of alleviating their gender dysphoria and providing them with appropriate medical services.

Referral for surgery

Surgical treatments for gender dysphoria can be initiated by a referral (one or two, depending on the type of surgery) from a qualified mental health professional. The mental health professional provides documentation—in the chart and/or referral letter—of the patient's personal and treatment history, progress, and eligibility. Mental health professionals who recommend surgery share the ethical and legal responsibility for that decision with the surgeon.

- One referral from a qualified mental health professional is needed for breast/chest surgery (e.g., mastectomy, chest reconstruction, or augmentation mammoplasty).
- Two referrals—from qualified mental health professionals who have independently assessed the patient—are needed for genital surgery (i.e., hysterectomy/salpingo-oophorectomy, orchiectomy, genital reconstructive surgeries). If the first referral is from the patient's psychotherapist, the second referral should be from a person who has only had an evaluative role with the patient. Two separate letters, or one letter signed by both (e.g., if practicing within the same clinic) may be sent. Each referral letter, however, is expected to cover the same topics in the areas outlined below.

The recommended content of the referral letters for surgery is as follows:

1. The client's general identifying characteristics;
2. Results of the client's psychosocial assessment, including any diagnoses;
3. The duration of the mental health professional's relationship with the client, including the type of evaluation and therapy or counseling to date;
4. An explanation that the criteria for surgery have been met, and a brief description of the clinical rationale for supporting the patient's request for surgery;
5. A statement about the fact that informed consent has been obtained from the patient;
6. A statement that the mental health professional is available for coordination of care and welcomes a phone call to establish this.

For providers working within a multidisciplinary specialty team, a letter may not be necessary, rather, the assessment and recommendation can be documented in the patient's chart.

Relationship of Mental Health Professionals with Hormone-Prescribing Physicians, Surgeons, and Other Health Professionals

It is ideal for mental health professionals to perform their work and periodically discuss progress and obtain peer consultation from other professionals (both in mental health care and other health disciplines) who are competent in the assessment and treatment of gender dysphoria. The relationship among professionals involved in a client's health care should remain collaborative, with coordination and clinical dialogue taking place as needed. Open and consistent communication may be necessary for consultation, referral, and management of postoperative concerns.

Tasks Related to Psychotherapy

1. Psychotherapy Is Not an Absolute Requirement for Hormone Therapy and Surgery

A mental health screening and/or assessment as outlined above is needed for referral to hormonal and surgical treatments for gender dysphoria. In contrast, psychotherapy—although highly recommended—is not a requirement.

The SOC do not recommend a minimum number of psychotherapy sessions prior to hormone therapy or surgery. The reasons for this are multifaceted (Lev, 2009). First, a minimum number of sessions tends to be construed as a hurdle, which discourages the genuine opportunity for personal growth. Second, mental health professionals can offer important support to clients throughout all phases of exploration of gender identity, gender expression, and possible transition—not just prior to any possible medical interventions. Third, clients and their psychotherapists differ in their abilities to attain similar goals in a specified time period.

2. Goals of Psychotherapy for Adults with Gender Concerns

The general goal of psychotherapy is to find ways to maximize a person's overall psychological well-being, quality of life, and self-fulfillment. Psychotherapy is not intended to alter a person's gender identity; rather, psychotherapy can help an individual to explore gender concerns and find ways to alleviate gender dysphoria, if present (Bockting et al., 2006; Bockting & Coleman, 2007; Fraser, 2009a; Lev, 2004). Typically, the overarching treatment goal is to help transsexual, transgender, and gender-nonconforming individuals achieve long-term comfort in their gender identity expression, with realistic chances for success in their relationships, education, and work. For additional details, see Fraser (Fraser, 2009c).

Therapy may consist of individual, couple, family, or group psychotherapy, the latter being particularly important to foster peer support.

3. Psychotherapy for Transsexual, Transgender, and Gender-Nonconforming Clients, Including Counseling and Support for Changes in Gender Role

Finding a comfortable gender role is, first and foremost, a psychosocial process. Psychotherapy can be invaluable in assisting transsexual, transgender, and gender-nonconforming individuals with all of the following: (i) clarifying and exploring gender identity and role, (ii) addressing the impact of stigma and minority stress on one's mental health and human development, and (iii) facilitating a coming-out process (Bockting & Coleman, 2007; Devor, 2004; Lev, 2004), which for some individuals may include changes in gender role expression and the use of feminizing/masculinizing medical interventions.

Mental health professionals can provide support and promote interpersonal skills and resilience in individuals and their families as they navigate a world that often is ill-prepared to accommodate and respect transgender, transsexual, and gender-nonconforming people. Psychotherapy can also aid in alleviating any coexisting mental health concerns (e.g., anxiety, depression) identified during screening and assessment.

For transsexual, transgender, and gender-nonconforming individuals who plan to change gender roles permanently and make a social gender role transition, mental health professionals can facilitate the development of an individualized plan with specific goals and timelines. While the experience of changing one's gender role differs from person to person, the social aspects of the experience are usually challenging—often more so than the physical aspects. Because changing gender role can have profound personal and social consequences, the decision to do so should include an awareness of what the familial, interpersonal, educational, vocational, economic, and legal challenges are likely to be, so that people can function successfully in their gender role.

Many transsexual, transgender, and gender-nonconforming people will present for care without ever having been related to, or accepted in, the gender role that is most congruent with their gender identity. Mental health professionals can help these clients to explore and anticipate the implications of changes in gender role, and to pace the process of implementing these changes. Psychotherapy can provide a space for clients to begin to express themselves in ways that are congruent with their gender identity and, for some clients, overcome fears about changes in gender expression. Calculated risks can be taken outside of therapy to gain experience and build confidence in the new role. Assistance with coming out to family and community (friends, school, workplace) can be provided.

Other transsexual, transgender, and gender-nonconforming individuals will present for care already having acquired experience (minimal, moderate, or extensive) living in a gender role that differs from that associated with their birth-assigned sex. Mental health professionals can help these clients to identify and work through potential challenges and foster optimal adjustment as they continue to express changes in their gender role.

4. Family Therapy or Support for Family Members

Decisions about changes in gender role and medical interventions for gender dysphoria have implications for, not only clients, but also their families (Emerson & Rosenfeld, 1996; Fraser, 2009a; Lev, 2004). Mental health professionals can assist clients with making thoughtful decisions about communicating with family members and others about their gender identity and treatment decisions. Family therapy may include work with spouses or partners, as well as with children and other members of a client's extended family.

Clients may also request assistance with their relationships and sexual health. For example, they may want to explore their sexuality and intimacy-related concerns.

Family therapy might be offered as part of the client's individual therapy and, if clinically appropriate, by the same provider. Alternatively, referrals can be made to other therapists with relevant expertise

for working with family members or to sources of peer support (e.g., in-person or offline support networks of partners or families).

5. Follow-Up Care Throughout Life

Mental health professionals may work with clients and their families at many stages of their lives. Psychotherapy may be helpful at different times and for various issues throughout the life cycle.

6. E-Therapy, Online Counseling, or Distance Counseling

Online or e-therapy has been shown to be particularly useful for people who have difficulty accessing competent in-person psychotherapeutic treatment and who may experience isolation and stigma (Derrig-Palumbo & Zeine, 2005; Fenichel et al., 2004; Fraser, 2009b). By extrapolation, e-therapy may be a useful modality for psychotherapy with transsexual, transgender, and gender-nonconforming people. E-therapy offers opportunities for potentially enhanced, expanded, creative, and tailored delivery of services; however, as a developing modality it may also carry unexpected risk. Telemedicine guidelines are clear in some disciplines in some parts of the United States (Fraser, 2009b; Maheu, Pulier, Wilhelm, McMenamin, & Brown-Connolly, 2005) but not all; the international situation is even less well-defined (Maheu et al., 2005). Until sufficient evidence-based data on this use of e-therapy is available, caution in its use is advised.

Mental health professionals engaging in e-therapy are advised to stay current with their particular licensing board, professional association, and country's regulations, as well as the most recent literature pertaining to this rapidly evolving medium. A more thorough description of the potential uses, processes, and ethical concerns related to e-therapy has been published (Fraser, 2009b).

Other Tasks of Mental Health Professionals

1. Educate and Advocate on Behalf of Clients Within Their Community (Schools, Workplaces, Other Organizations) and Assist Clients with Making Changes in Identity Documents

Transsexual, transgender, and gender-nonconforming people may face challenges in their professional, educational, and other types of settings as they actualize their gender identity and expression (Lev, 2004, 2009). Mental health professionals can play an important role by educating people in these settings regarding gender nonconformity and by advocating on behalf of their clients (Currah, Juang, & Minter, 2006; Currah & Minter, 2000). This role may involve consultation

with school counselors, teachers, and administrators, human resources staff, personnel managers and employers, and representatives from other organizations and institutions. In addition, health providers may be called upon to support changes in a client's name and/or gender marker on identity documents such as passports, driver's licenses, birth certificates, and diplomas.

2. Provide Information and Referral for Peer Support

For some transsexual, transgender, and gender-nonconforming people, an experience in peer support groups may be more instructive regarding options for gender expression than anything individual psychotherapy could offer (Rachlin, 2002). Both experiences are potentially valuable, and all people exploring gender issues should be encouraged to participate in community activities, if possible. Resources for peer support and information should be made available.

Culture and Its Ramifications for Assessment and Psychotherapy

Health professionals work in enormously different environments across the world. Forms of distress that cause people to seek professional assistance in any culture are understood and classified by people in terms that are products of their own cultures (Frank & Frank, 1993). Cultural settings also largely determine how such conditions are understood by mental health professionals. Cultural differences related to gender identity and expression can affect patients, mental health professionals, and accepted psychotherapy practice. WPATH recognizes that the SOC have grown out of a Western tradition and may need to be adapted depending on the cultural context.

Ethical Guidelines Related to Mental Health Care

Mental health professionals need to be certified or licensed to practice in a given country according to that country's professional regulations (Fraser, 2009b; Pope & Vasquez, 2011). Professionals must adhere to the ethical codes of their professional licensing or certifying organizations in all of their work with transsexual, transgender, and gender-nonconforming clients.

Treatment aimed at trying to change a person's gender identity and lived gender expression to become more congruent with sex assigned at birth has been attempted in the past (Gelder & Marks, 1969; Greenson, 1964), yet without success, particularly in the long-term (Cohen-Kettenis & Kuiper, 1984; Pauly, 1965). Such treatment is no longer considered ethical.

If mental health professionals are uncomfortable with, or inexperienced in, working with transsexual, transgender, and gender-nonconforming individuals and their families, they should refer clients to a competent provider or, at minimum, consult with an expert peer. If no local practitioners are available, consultation may be done via telehealth methods, assuming local requirements for distance consultation are met.

Issues of Access to Care

Qualified mental health professionals are not universally available; thus, access to quality care might be limited. WPATH aims to improve access and provides regular continuing education opportunities to train professionals from various disciplines to provide quality, transgender-specific health care. Providing mental health care from a distance through the use of technology may be one way to improve access (Fraser, 2009b).

In many places around the world, access to health care for transsexual, transgender, and gender-nonconforming people is also limited by a lack of health insurance or other means to pay for needed care. WPATH urges health insurance companies and other third-party payers to cover the medically necessary treatments to alleviate gender dysphoria (American Medical Association, 2008; Anton, 2009; The World Professional Association for Transgender Health, 2008).

When faced with a client who is unable to access services, referral to available peer support resources (offline and online) is recommended. Finally, harm-reduction approaches might be indicated to assist clients with making healthy decisions to improve their lives.

VIII

Hormone Therapy

Medical Necessity of Hormone Therapy

Feminizing/masculinizing hormone therapy—the administration of exogenous endocrine agents to induce feminizing or masculinizing changes—is a medically necessary intervention for many transsexual, transgender, and gender-nonconforming individuals with gender dysphoria

(Newfield, Hart, Dibble, & Kohler, 2006; Pfäfflin & Junge, 1998). Some people seek maximum feminization/masculinization, while others experience relief with an androgynous presentation resulting from hormonal minimization of existing secondary sex characteristics (Factor & Rothblum, 2008). Evidence for the psychosocial outcomes of hormone therapy is summarized in Appendix D.

Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Hormone therapy can provide significant comfort to patients who do not wish to make a social gender role transition or undergo surgery, or who are unable to do so (Meyer III, 2009). Hormone therapy is a recommended criterion for some, but not all, surgical treatments for gender dysphoria (see section XI and Appendix C).

Criteria for Hormone Therapy

Initiation of hormone therapy may be undertaken after a psychosocial assessment has been conducted and informed consent has been obtained by a qualified health professional, as outlined in section VII of the SOC. A referral is required from the mental health professional who performed the assessment, unless the assessment was done by a hormone provider who is also qualified in this area.

The criteria for hormone therapy are as follows:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC outlined in section VI);
4. If significant medical or mental health concerns are present, they must be reasonably well-controlled.

As noted in section VII of the SOC, the presence of coexisting mental health concerns does not necessarily preclude access to feminizing/masculinizing hormones; rather, these concerns need to be managed prior to, or concurrent with, treatment of gender dysphoria.

In selected circumstances, it can be acceptable practice to provide hormones to patients who have not fulfilled these criteria. Examples include facilitating the provision of monitored therapy using hormones of known quality as an alternative to illicit or unsupervised hormone use or to patients

who have already established themselves in their affirmed gender and who have a history of prior hormone use. It is unethical to deny availability or eligibility for hormone therapy solely on the basis of blood seropositivity for blood-borne infections such as HIV or hepatitis B or C.

In rare cases, hormone therapy may be contraindicated due to serious individual health conditions. Health professionals should assist these patients with accessing nonhormonal interventions for gender dysphoria. A qualified mental health professional familiar with the patient is an excellent resource in these circumstances.

Informed Consent

Feminizing/masculinizing hormone therapy may lead to irreversible physical changes. Thus, hormone therapy should be provided only to those who are legally able to provide informed consent. This includes people who have been declared by a court to be emancipated minors, incarcerated people, and cognitively impaired people who are considered competent to participate in their medical decisions (Bockting et al., 2006). Providers should document in the medical record that comprehensive information has been provided and understood about all relevant aspects of the hormone therapy, including both possible benefits and risks and the impact on reproductive capacity.

Relationship Between the *Standards of Care* and Informed Consent Model Protocols

A number of community health centers in the United States have developed protocols for providing hormone therapy based on an approach that has become known as the Informed Consent Model (Callen Lorde Community Health Center, 2000, 2011; Fenway Community Health Transgender Health Program, 2007; Tom Waddell Health Center, 2006). These protocols are consistent with the guidelines presented in the WPATH *Standards of Care, Version 7*. The SOC are flexible clinical guidelines; they allow for tailoring of interventions to the needs of the individual receiving services and for tailoring of protocols to the approach and setting in which these services are provided (Ehrbar & Gorton, 2010).

Obtaining informed consent for hormone therapy is an important task of providers to ensure that patients understand the psychological and physical benefits and risks of hormone therapy, as well as its psychosocial implications. Providers prescribing the hormones or health professionals recommending the hormones should have the knowledge and experience to assess gender

dysphoria. They should inform individuals of the particular benefits, limitations, and risks of hormones, given the patient's age, previous experience with hormones, and concurrent physical or mental health concerns.

Screening for and addressing acute or current mental health concerns is an important part of the informed consent process. This may be done by a mental health professional or by an appropriately trained prescribing provider (see section VII of the SOC). The same provider or another appropriately trained member of the health care team (e.g., a nurse) can address the psychosocial implications of taking hormones when necessary (e.g., the impact of masculinization/feminization on how one is perceived and its potential impact on relationships with family, friends, and coworkers). If indicated, these providers will make referrals for psychotherapy and for the assessment and treatment of coexisting mental health concerns such as anxiety or depression.

The difference between the Informed Consent Model and *SOC, Version 7*, is that the SOC puts greater emphasis on the important role that mental health professionals can play in alleviating gender dysphoria and facilitating changes in gender role and psychosocial adjustment. This may include a comprehensive mental health assessment and psychotherapy, when indicated. In the Informed Consent Model, the focus is on obtaining informed consent as the threshold for the initiation of hormone therapy in a multidisciplinary, harm-reduction environment. Less emphasis is placed on the provision of mental health care until the patient requests it, unless significant mental health concerns are identified that would need to be addressed before hormone prescription.

Physical Effects of Hormone Therapy

Feminizing/masculinizing hormone therapy will induce physical changes that are more congruent with a patient's gender identity.

- In FtM patients, the following physical changes are expected to occur: deepened voice, clitoral enlargement (variable), growth in facial and body hair, cessation of menses, atrophy of breast tissue, and decreased percentage of body fat compared to muscle mass.
- In MtF patients, the following physical changes are expected to occur: breast growth (variable), decreased erectile function, decreased testicular size, and increased percentage of body fat compared to muscle mass.

Most physical changes, whether feminizing or masculinizing, occur over the course of two years. The amount of physical change and the exact timeline of effects can be highly variable. Tables 1a and 1b outline the approximate time course of these physical changes.

TABLE 1A: EFFECTS AND EXPECTED TIME COURSE OF MASCULINIZING HORMONES ^A

Effect	Expected onset ^B	Expected maximum effect ^B
Skin oiliness/acne	1–6 months	1–2 years
Facial/body hair growth	3–6 months	3–5 years
Scalp hair loss	>12 months ^C	Variable
Increased muscle mass/strength	6–12 months	2–5 years ^D
Body fat redistribution	3–6 months	2–5 years
Cessation of menses	2–6 months	n/a
Clitoral enlargement	3–6 months	1–2 years
Vaginal atrophy	3–6 months	1–2 years
Deepened voice	3–12 months	1–2 years

^A Adapted with permission from Hembree et al.(2009). Copyright 2009, The Endocrine Society.

^B Estimates represent published and unpublished clinical observations.

^C Highly dependent on age and inheritance; may be minimal.

^D Significantly dependent on amount of exercise.

TABLE 1B: EFFECTS AND EXPECTED TIME COURSE OF FEMINIZING HORMONES ^A

Effect	Expected onset ^B	Expected maximum effect ^B
Body fat redistribution	3–6 months	2–5 years
Decreased muscle mass/ strength	3–6 months	1–2 years ^C
Softening of skin/decreased oiliness	3–6 months	Unknown
Decreased libido	1–3 months	1–2 years
Decreased spontaneous erections	1–3 months	3–6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 months	2–3 years
Decreased testicular volume	3–6 months	2–3 years
Decreased sperm production	Variable	Variable
Thinning and slowed growth of body and facial hair	6–12 months	> 3 years ^D
Male pattern baldness	No regrowth, loss stops 1–3 months	1–2 years

^A Adapted with permission from Hembree et al. (2009). Copyright 2009, The Endocrine Society.

^B Estimates represent published and unpublished clinical observations.

^C Significantly dependent on amount of exercise.

^D Complete removal of male facial and body hair requires electrolysis, laser treatment, or both.

The degree and rate of physical effects depends in part on the dose, route of administration, and medications used, which are selected in accordance with a patient's specific medical goals (e.g., changes in gender role expression, plans for sex reassignment) and medical risk profile. There is no current evidence that response to hormone therapy—with the possible exception of voice deepening in FtM persons—can be reliably predicted based on age, body habitus, ethnicity, or family appearance. All other factors being equal, there is no evidence to suggest that any medically approved type or method of administering hormones is more effective than any other in producing the desired physical changes.

Risks of Hormone Therapy

All medical interventions carry risks. The likelihood of a serious adverse event is dependent on numerous factors: the medication itself, dose, route of administration, and a patient's clinical characteristics (age, comorbidities, family history, health habits). It is thus impossible to predict whether a given adverse effect will happen in an individual patient.

The risks associated with feminizing/masculinizing hormone therapy for the transsexual, transgender, and gender-nonconforming population as a whole are summarized in Table 2. Based on the level of evidence, risks are categorized as follows: (i) likely increased risk with hormone therapy, (ii) possibly increased risk with hormone therapy, or (iii) inconclusive or no increased risk. Items in the last category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Additional detail about these risks can be found in Appendix B, which is based on two comprehensive, evidence-based literature reviews of masculinizing/feminizing hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009), along with a large cohort study (Asscheman et al., 2011). These reviews can serve as detailed references for providers, along with other widely recognized, published clinical materials (Dahl, Feldman, Goldberg, & Jaber, 2006; Ettner, Monstrey, & Eyler, 2007).

TABLE 2: RISKS ASSOCIATED WITH HORMONE THERAPY. BOLDED ITEMS ARE CLINICALLY SIGNIFICANT

Risk Level	Feminizing hormones	Masculinizing hormones
Likely increased risk	Venous thromboembolic disease^A Gallstones Elevated liver enzymes Weight gain Hypertriglyceridemia	Polycythemia Weight gain Acne Androgenic alopecia (balding) Sleep apnea
Likely increased risk with presence of additional risk factors ^B	Cardiovascular disease	
Possible increased risk	Hypertension Hyperprolactinemia or prolactinoma	Elevated liver enzymes Hyperlipidemia
Possible increased risk with presence of additional risk factors ^B	Type 2 diabetes^A	Destabilization of certain psychiatric disorders^C Cardiovascular disease Hypertension Type 2 diabetes
No increased risk or inconclusive	Breast cancer	Loss of bone density Breast cancer Cervical cancer Ovarian cancer Uterine cancer

* **Note:** Risk is greater with oral estrogen administration than with transdermal estrogen administration.

^A Risk is greater with oral estrogen administration than with transdermal estrogen administration.

^B Additional risk factors include age.

^C Includes bipolar, schizoaffective, and other disorders that may include manic or psychotic symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

Competency of Hormone-Prescribing Physicians, Relationship with Other Health Professionals

Feminizing/masculinizing hormone therapy is best undertaken in the context of a complete approach to health care that includes comprehensive primary care and a coordinated approach to psychosocial issues (Feldman & Safer, 2009). While psychotherapy or ongoing counseling is not required for the initiation of hormone therapy, if a therapist is involved, then regular communication among health professionals is advised (with the patient's consent) to ensure that the transition process is going well, both physically and psychosocially.

With appropriate training, feminizing/masculinizing hormone therapy can be managed by a variety of providers, including nurse practitioners, physician assistants, and primary care physicians (Dahl et al., 2006). Medical visits relating to hormone maintenance provide an opportunity to deliver broader care to a population that is often medically underserved (Clements, Wilkinson, Kitano, & Marx, 1999; Feldman, 2007; Xavier, 2000). Many of the screening tasks and management of comorbidities associated with long-term hormone use, such as cardiovascular risk factors and cancer screening, fall more uniformly within the scope of primary care rather than specialist care (American Academy of Family Physicians, 2005; Eyler, 2007; World Health Organization, 2008), particularly in locations where dedicated gender teams or specialized physicians are not available.

Given the multidisciplinary needs of transsexual, transgender, and gender-nonconforming people seeking hormone therapy, as well as the difficulties associated with fragmentation of care in general (World Health Organization, 2008), WPATH strongly encourages the increased training and involvement of primary care providers in the area of feminizing/masculinizing hormone therapy. If hormones are prescribed by a specialist, there should be close communication with the patient's primary care provider. Conversely, an experienced hormone provider or endocrinologist should be involved if the primary care physician has no experience with this type of hormone therapy, or if the patient has a pre-existing metabolic or endocrine disorder that could be affected by endocrine therapy.

While formal training programs in transgender medicine do not yet exist, hormone providers have a responsibility to obtain appropriate knowledge and experience in this field. Clinicians can increase their experience and comfort in providing feminizing/masculinizing hormone therapy by co-managing care or consulting with a more experienced provider, or by providing more limited types of hormone therapy before progressing to initiation of hormone therapy. Because this field of medicine is evolving, clinicians should become familiar and keep current with the medical literature, and discuss emerging issues with colleagues. Such discussions might occur through networks established by WPATH and other national/local organizations.

Responsibilities of Hormone-Prescribing Physicians

In general, clinicians who prescribe hormone therapy should engage in the following tasks:

1. Perform an initial evaluation that includes discussion of a patient's physical transition goals, health history, physical examination, risk assessment, and relevant laboratory tests.
2. Discuss with patients the expected effects of feminizing/masculinizing medications and the possible adverse health effects. These effects can include a reduction in fertility (Feldman & Safer, 2009; Hembree et al., 2009). Therefore, reproductive options should be discussed with patients before starting hormone therapy (see section IX).
3. Confirm that patients have the capacity to understand the risks and benefits of treatment and are capable of making an informed decision about medical care.
4. Provide ongoing medical monitoring, including regular physical and laboratory examination to monitor hormone effectiveness and side effects.
5. Communicate as needed with a patient's primary care provider, mental health professional, and surgeon.
6. If needed, provide patients with a brief written statement indicating that they are under medical supervision and care that includes feminizing/masculinizing hormone therapy. Particularly during the early phases of hormone treatment, a patient may wish to carry this statement at all times to help prevent difficulties with the police and other authorities.

Depending on the clinical situation for providing hormones (see below), some of these responsibilities are less relevant. Thus, the degree of counseling, physical examinations, and laboratory evaluations should be individualized to a patient's needs.

Clinical Situations for Hormone Therapy

There are circumstances in which clinicians may be called upon to provide hormones without necessarily initiating or maintaining long-term feminizing/masculinizing hormone therapy. By acknowledging these different clinical situations (see below, from least to highest level of complexity), it may be possible to involve clinicians in feminizing/masculinizing hormone therapy who might not otherwise feel able to offer this treatment.

1. Bridging

Whether prescribed by another clinician or obtained through other means (e.g., purchased over the Internet), patients may present for care already on hormone therapy. Clinicians can provide a limited (1–6 month) prescription for hormones while helping patients find a provider who can prescribe long-term hormone therapy. Providers should assess a patient's current regimen for safety and drug interactions and substitute safer medications or doses when indicated (Dahl et al., 2006; Feldman & Safer, 2009). If hormones were previously prescribed, medical records should be requested (with the patient's permission) to obtain the results of baseline examinations and laboratory tests and any adverse events. Hormone providers should also communicate with any mental health professional who is currently involved in a patient's care. If a patient has never had a psychosocial assessment as recommended by the SOC (see section VII), clinicians should refer the patient to a qualified mental health professional if appropriate and feasible (Feldman & Safer, 2009). Providers who prescribe bridging hormones need to work with patients to establish limits as to the duration of bridging therapy.

2. Hormone Therapy Following Gonad Removal

Hormone replacement with estrogen or testosterone is usually continued lifelong after an oophorectomy or orchiectomy, unless medical contraindications arise. Because hormone doses are often decreased after these surgeries (Basson, 2001; Levy, Crown, & Reid, 2003; Moore, Wisniewski, & Dobs, 2003) and only adjusted for age and comorbid health concerns, hormone management in this situation is quite similar to hormone replacement in any hypogonadal patient.

3. Hormone Maintenance Prior to Gonad Removal

Once patients have achieved maximal feminizing/masculinizing benefits from hormones (typically two or more years), they remain on a maintenance dose. The maintenance dose is then adjusted for changes in health conditions, aging, or other considerations such as lifestyle changes (Dahl et al., 2006). When a patient on maintenance hormones presents for care, the provider should assess the patient's current regimen for safety and drug interactions and substitute safer medications or doses when indicated. The patient should continue to be monitored by physical examinations and laboratory testing on a regular basis, as outlined in the literature (Feldman & Safer, 2009; Hembree et al., 2009). The dose and form of hormones should be revisited regularly with any changes in the patient's health status and available evidence on the potential long-term risks of hormones (See *Hormone Regimens*, below).

4. Initiating Hormonal Feminization/Masculinization

This clinical situation requires the greatest commitment in terms of provider time and expertise. Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Although a wide variety of hormone regimens have been published (Dahl et al., 2006; Hembree et al., 2009; Moore et al., 2003), there are no published reports of randomized clinical trials comparing safety and efficacy. Despite this variation, a reasonable framework for initial risk assessment and ongoing monitoring of hormone therapy can be constructed, based on the efficacy and safety evidence presented above.

Risk Assessment and Modification for Initiating Hormone Therapy

The initial evaluation for hormone therapy assesses a patient's clinical goals and risk factors for hormone-related adverse events. During the risk assessment, the patient and clinician should develop a plan for reducing risks wherever possible, either prior to initiating therapy or as part of ongoing harm reduction.

All assessments should include a thorough physical exam, including weight, height, and blood pressure. The need for breast, genital, and rectal exams, which are sensitive issues for most transsexual, transgender, and gender-nonconforming patients, should be based on individual risks and preventive health care needs (Feldman & Goldberg, 2006; Feldman, 2007).

Preventive Care

Hormone providers should address preventive health care with patients, particularly if a patient does not have a primary care provider. Depending on a patient's age and risk profile, there may be appropriate screening tests or exams for conditions affected by hormone therapy. Ideally, these screening tests should be carried out prior to the start of hormone therapy.

Risk Assessment and Modification for Feminizing Hormone Therapy (MtF)

There are no absolute contraindications to feminizing therapy per se, but absolute contraindications exist for the different feminizing agents, particularly estrogen. These include previous venous thrombotic events related to an underlying hypercoagulable condition, history of estrogen-sensitive neoplasm, and end-stage chronic liver disease (Gharib et al., 2005).

Other medical conditions, as noted in Table 2 and Appendix B, can be exacerbated by estrogen or androgen blockade, and therefore should be evaluated and reasonably well controlled prior to starting hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009). Clinicians should particularly attend to tobacco use, as it is associated with increased risk of venous thrombosis, which is further increased with estrogen use. Consultation with a cardiologist may be advisable for patients with known cardio- or cerebrovascular disease.

Baseline laboratory values are important to both assess initial risk and evaluate possible future adverse events. Initial labs should be based on the risks of feminizing hormone therapy outlined in Table 2, as well as individual patient risk factors, including family history. Suggested initial lab panels have been published (Feldman & Safer, 2009; Hembree et al., 2009). These can be modified for patients or health care systems with limited resources, and in otherwise healthy patients.

Risk Assessment and Modification for Masculinizing Hormone Therapy (FtM)

Absolute contraindications to testosterone therapy include pregnancy, unstable coronary artery disease, and untreated polycythemia with a hematocrit of 55% or higher (Carnegie, 2004). Because the aromatization of testosterone to estrogen may increase risk in patients with a history of breast or other estrogen dependent cancers (Moore et al., 2003), consultation with an oncologist may be indicated prior to hormone use. Comorbid conditions likely to be exacerbated by testosterone use should be evaluated and treated, ideally prior to starting hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009). Consultation with a cardiologist may be advisable for patients with known cardio- or cerebrovascular disease. (Dhejne et al., 2011).

An increased prevalence of polycystic ovarian syndrome (PCOS) has been noted among FtM patients even in the absence of testosterone use (Baba et al., 2007; Balen, Schachter, Montgomery, Reid, & Jacobs, 1993; Bosinski et al., 1997). While there is no evidence that PCOS is related to the development of a transsexual, transgender, or gender-nonconforming identity, PCOS is associated with increased risk of diabetes, cardiac disease, high blood pressure, and ovarian and endometrial cancers (Cattrall & Healy, 2004). Signs and symptoms of PCOS should be evaluated prior to initiating testosterone therapy, as testosterone may affect many of these conditions. Testosterone can affect the developing fetus (*Physicians' Desk Reference*, 2010), and patients at risk of becoming pregnant require highly effective birth control.

Baseline laboratory values are important to both assess initial risk and evaluate possible future adverse events. Initial labs should be based on the risks of masculinizing hormone therapy outlined in Table 2, as well as individual patient risk factors, including family history. Suggested initial lab panels have been published (Feldman & Safer, 2009; Hembree et al., 2009). These can be modified for patients or health care systems with limited resources, and in otherwise healthy patients.

Clinical Monitoring During Hormone Therapy for Efficacy and Adverse Events

The purpose of clinical monitoring during hormone use is to assess the degree of feminization/masculinization and the possible presence of adverse effects of medication. However, as with the monitoring of any long-term medication, monitoring should take place in the context of comprehensive health care. Suggested clinical monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009). Patients with comorbid medical conditions may need to be monitored more frequently. Healthy patients in geographically remote or resource-poor areas may be able to use alternative strategies, such as telehealth, or cooperation with local providers such as nurses and physician assistants. In the absence of other indications, health professionals may prioritize monitoring for those risks that are either likely to be increased by hormone therapy or possibly increased by hormone therapy but clinically serious in nature.

Efficacy and Risk Monitoring During Feminizing Hormone Therapy (MtF)

The best assessment of hormone efficacy is clinical response: Is a patient developing a feminized body while minimizing masculine characteristics, consistent with that patient's gender goals? In order to more rapidly predict the hormone dosages that will achieve clinical response, one can measure testosterone levels for suppression below the upper limit of the normal female range and estradiol levels within a premenopausal female range but well below supraphysiologic levels (Feldman & Safer, 2009; Hembree et al., 2009).

Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs of cardiovascular impairment and venous thromboembolism (VTE) through measurement of blood pressure, weight, and pulse; heart and lung exams; and examination of the extremities for peripheral edema, localized swelling, or pain (Feldman & Safer, 2009). Laboratory monitoring should be based on the risks of hormone therapy described above, a patient's individual comorbidities and risk factors, and the specific hormone regimen itself. Specific lab-monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009).

Efficacy and Risk Monitoring During Masculinizing Hormone Therapy (FtM)

The best assessment of hormone efficacy is clinical response: Is a patient developing a masculinized body while minimizing feminine characteristics, consistent with that patient's gender goals? Clinicians can achieve a good clinical response with the least likelihood of adverse events by maintaining testosterone levels within the normal male range while avoiding supraphysiological

levels (Dahl et al., 2006; Hembree et al., 2009). For patients using intramuscular (IM) testosterone cypionate or enanthate, some clinicians check trough levels while others prefer midcycle levels (Dahl et al., 2006; Hembree et al., 2009; Tangpricha, Turner, Malabanan, & Holick, 2001; Tangpricha, Ducharme, Barber, & Chipkin, 2003).

Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs and symptoms of excessive weight gain, acne, uterine break-through bleeding, and cardiovascular impairment, as well as psychiatric symptoms in at-risk patients. Physical examinations should include measurement of blood pressure, weight, and pulse; and heart, lung, and skin exams (Feldman & Safer, 2009). Laboratory monitoring should be based on the risks of hormone therapy described above, a patient's individual comorbidities and risk factors, and the specific hormone regimen itself. Specific lab monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009).

Hormone Regimens

To date, no controlled clinical trials of any feminizing/masculinizing hormone regimen have been conducted to evaluate safety or efficacy in producing physical transition. As a result, wide variation in doses and types of hormones have been published in the medical literature (Moore et al., 2003; Tangpricha et al., 2003; van Kesteren, Asscheman, Megens, & Gooren, 1997). In addition, access to particular medications may be limited by a patient's geographical location and/or social or economic situations. For these reasons, WPATH does not describe or endorse a particular feminizing/masculinizing hormone regimen. Rather, the medication classes and routes of administration used in most published regimens are broadly reviewed.

As outlined above, there are demonstrated safety differences in individual elements of various regimens. The Endocrine Society Guidelines (Hembree et al., 2009) and Feldman and Safer (2009) provide specific guidance regarding the types of hormones and suggested dosing to maintain levels within physiologic ranges for a patient's desired gender expression (based on goals of full feminization/masculinization). It is strongly recommend that hormone providers regularly review the literature for new information and use those medications that safely meet individual patient needs with available local resources.

Regimens for Feminizing Hormone Therapy (MtF)Estrogen

Use of oral estrogen, and specifically ethinyl estradiol, appears to increase the risk of VTE. Because of this safety concern, ethinyl estradiol is not recommended for feminizing hormone therapy. Transdermal estrogen is recommended for those patients with risks factors for VTE. The risk of adverse events increases with higher doses, particular doses resulting in supraphysiologic levels (Hembree et al., 2009). Patients with co-morbid conditions that can be affected by estrogen should avoid oral estrogen if possible and be started at lower levels. Some patients may not be able to safely use the levels of estrogen needed to get the desired results. This possibility needs to be discussed with patients well in advance of starting hormone therapy.

Androgen-reducing medications (“anti-androgens”)

A combination of estrogen and “anti-androgens” is the most commonly studied regimen for feminization. Androgen-reducing medications, from a variety of classes of drugs, have the effect of reducing either endogenous testosterone levels or testosterone activity, and thus diminishing masculine characteristics such as body hair. They minimize the dosage of estrogen needed to suppress testosterone, thereby reducing the risks associated with high-dose exogenous estrogen (Prior, Vigna, Watson, Diewold, & Robinow, 1986; Prior, Vigna, & Watson, 1989).

Common anti-androgens include the following:

- Spironolactone, an antihypertensive agent, directly inhibits testosterone secretion and androgen binding to the androgen receptor. Blood pressure and electrolytes need to be monitored because of the potential for hyperkalemia.
- Cyproterone acetate is a progestational compound with anti-androgenic properties. This medication is not approved in the United States because of concerns over potential hepatotoxicity, but it is widely used elsewhere (De Cuypere et al., 2005).
- GnRH agonists (e.g., goserelin, buserelin, triptorelin) are neurohormones that block the gonadotropin-releasing hormone receptor, thus blocking the release of follicle stimulating hormone and luteinizing hormone. This leads to highly effective gonadal blockade. However, these medications are expensive and only available as injectables or implants.
- 5-alpha reductase inhibitors (finasteride and dutasteride) block the conversion of testosterone to the more active agent, 5-alpha-dihydrotestosterone. These medications have beneficial effects on scalp hair loss, body hair growth, sebaceous glands, and skin consistency.

Cyproterone and spironolactone are the most commonly used anti-androgens and are likely the most cost-effective.

Progestins

With the exception of cyproterone, the inclusion of progestins in feminizing hormone therapy is controversial (Oriel, 2000). Because progestins play a role in mammary development on a cellular level, some clinicians believe that these agents are necessary for full breast development (Basson & Prior, 1998; Oriel, 2000). However, a clinical comparison of feminization regimens with and without progestins found that the addition of progestins neither enhanced breast growth nor lowered serum levels of free testosterone (Meyer et al., 1986). There are concerns regarding potential adverse effects of progestins, including depression, weight gain, and lipid changes (Meyer et al., 1986; Tangpricha et al., 2003). Progestins (especially medroxyprogesterone) are also suspected to increase breast cancer risk and cardiovascular risk in women (Rossouw et al., 2002). Micronized progesterone may be better tolerated and have a more favorable impact on the lipid profile than medroxyprogesterone does (de Lignières, 1999; Fitzpatrick, Pace, & Wiita, 2000).

Regimens for Masculinizing Hormone Therapy (FtM)

Testosterone

Testosterone generally can be given orally, transdermally, or parenterally (IM), although buccal and implantable preparations are also available. Oral testosterone undecanoate, available outside the United States, results in lower serum testosterone levels than nonoral preparations and has limited efficacy in suppressing menses (Feldman, 2005, April; Moore et al., 2003). Because intramuscular testosterone cypionate or enanthate are often administered every 2–4 weeks, some patients may notice cyclic variation in effects (e.g., fatigue and irritability at the end of the injection cycle, aggression or expansive mood at the beginning of the injection cycle), as well as more time outside the normal physiologic levels (Jockenhövel, 2004). This may be mitigated by using a lower but more frequent dosage schedule or by using a daily transdermal preparation (Dobs et al., 1999; Jockenhövel, 2004; Nieschlag et al., 2004). Intramuscular testosterone undecanoate (not currently available in the United States) maintains stable, physiologic testosterone levels over approximately 12 weeks and has been effective in both the setting of hypogonadism and in FtM individuals (Mueller, Kiesewetter, Binder, Beckmann, & Dittrich, 2007; Zitzmann, Saad, & Nieschlag, 2006). There is evidence that transdermal and intramuscular testosterone achieve similar masculinizing results, although the timeframe may be somewhat slower with transdermal preparations (Feldman, 2005, April). Especially as patients age, the goal is to use the lowest dose needed to maintain the desired clinical result, with appropriate precautions being made to maintain bone density.

Other agents

Progestins, most commonly medroxyprogesterone, can be used for a short period of time to assist with menstrual cessation early in hormone therapy. GnRH agonists can be used similarly, as well as for refractory uterine bleeding in patients without an underlying gynecological abnormality.

Bioidentical and Compounded Hormones

As discussion surrounding the use of bioidentical hormones in postmenopausal hormone replacement has heightened, interest has also increased in the use of similar compounds in feminizing/masculinizing hormone therapy. There is no evidence that custom compounded bioidentical hormones are safer or more effective than government agency-approved bioidentical hormones (Sood, Shuster, Smith, Vincent, & Jatoi, 2011). Therefore, it has been advised by the North American Menopause Society (2010) and others to assume that, whether the hormone is from a compounding pharmacy or not, if the active ingredients are similar, it should have a similar side-effect profile. WPATH concurs with this assessment.

IX

Reproductive Health

Many transgender, transsexual, and gender-nonconforming people will want to have children. Because feminizing/masculinizing hormone therapy limits fertility (Darney, 2008; Zhang, Gu, Wang, Cui, & Bremner, 1999), it is desirable for patients to make decisions concerning fertility before starting hormone therapy or undergoing surgery to remove/alter their reproductive organs. Cases are known of people who received hormone therapy and genital surgery and later regretted their inability to parent genetically related children (De Sutter, Kira, Verschoor, & Hotimsky, 2002).

Health care professionals—including mental health professionals recommending hormone therapy or surgery, hormone-prescribing physicians, and surgeons—should discuss reproductive options with patients prior to initiation of these medical treatments for gender dysphoria. These discussions should occur even if patients are not interested in these issues at the time of treatment, which may be more common for younger patients (De Sutter, 2009). Early discussions are desirable, but not always possible. If an individual has not had complete sex reassignment surgery, it may be possible to stop hormones long enough for natal hormones to recover, allowing

the production of mature gametes (Payer, Meyer, & Walker, 1979; Van den Broecke, Van der Elst, Liu, Hovatta, & Dhont, 2001).

Besides debate and opinion papers, very few research papers have been published on the reproductive health issues of individuals receiving different medical treatments for gender dysphoria. Another group who faces the need to preserve reproductive function in light of loss or damage to their gonads are people with malignancies that require removal of reproductive organs or use of damaging radiation or chemotherapy. Lessons learned from that group can be applied to people treated for gender dysphoria.

MtF patients, especially those who have not already reproduced, should be informed about sperm-preservation options and encouraged to consider banking their sperm prior to hormone therapy. In a study examining testes that were exposed to high-dose estrogen (Payer et al., 1979), findings suggest that stopping estrogen may allow the testes to recover. In an article reporting on the opinions of MtF individuals towards sperm freezing (De Sutter et al., 2002), the vast majority of 121 survey respondents felt that the availability of freezing sperm should be discussed and offered by the medical world. Sperm should be collected before hormone therapy or after stopping the therapy until the sperm count rises again. Cryopreservation should be discussed even if there is poor semen quality. In adults with azoospermia, a testicular biopsy with subsequent cryopreservation of biopsied material for sperm is possible, but may not be successful.

Reproductive options for FtM patients might include oocyte (egg) or embryo freezing. The frozen gametes and embryo could later be used with a surrogate woman to carry to pregnancy. Studies of women with polycystic ovarian disease suggest that the ovary can recover in part from the effects of high testosterone levels (Hunter & Sterrett, 2000). Stopping the testosterone briefly might allow for ovaries to recover enough to release eggs; success likely depends on the patient's age and duration of testosterone treatment. While not systematically studied, some FtM individuals are doing exactly that, and some have been able to become pregnant and deliver children (More, 1998).

Patients should be advised that these techniques are not available everywhere and can be very costly. Transsexual, transgender, and gender-nonconforming people should not be refused reproductive options for any reason.

A special group of individuals are prepubertal or pubertal adolescents who will never develop reproductive function in their natal sex due to blockers or cross-gender hormones. At this time there is no technique for preserving function from the gonads of these individuals.



Voice and Communication Therapy

Communication, both verbal and nonverbal, is an important aspect of human behavior and gender expression. Transsexual, transgender, and gender-nonconforming people might seek the assistance of a voice and communication specialist to develop vocal characteristics (e.g., pitch, intonation, resonance, speech rate, phrasing patterns) and non-verbal communication patterns (e.g., gestures, posture/movement, facial expressions) that facilitate comfort with their gender identity. Voice and communication therapy may help to alleviate gender dysphoria and be a positive and motivating step towards achieving one's goals for gender role expression.

Competency of Voice and Communication Specialists Working with Transsexual, Transgender, and Gender-Nonconforming Clients

Specialists may include speech-language pathologists, speech therapists, and speech-voice clinicians. In most countries the professional association for speech-language pathologists requires specific qualifications and credentials for membership. In some countries the government regulates practice through licensing, certification, or registration processes (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

The following are recommended minimum credentials for voice and communication specialists working with transsexual, transgender, and gender-nonconforming clients:

1. Specialized training and competence in the assessment and development of communication skills in transsexual, transgender, and gender-nonconforming clients.
2. A basic understanding of transgender health, including hormonal and surgical treatments for feminization/masculinization and trans-specific psychosocial issues as outlined in the SOC; and familiarity with basic sensitivity protocols such as the use of preferred gender pronoun and name (Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

3. Continuing education in the assessment and development of communication skills in transsexual, transgender, and gender-nonconforming clients. This may include attendance at professional meetings, workshops, or seminars; participation in research related to gender identity issues; independent study; or mentoring from an experienced, certified clinician.

Other professionals such as vocal coaches, theatre professionals, singing teachers, and movement experts may play a valuable adjunct role. Such professionals will ideally have experience working with, or be actively collaborating with, speech-language pathologists.

Assessment and Treatment Considerations

The overall purpose of voice and communication therapy is to help clients adapt their voice and communication in a way that is both safe and authentic, resulting in communication patterns that clients feel are congruent with their gender identity and that reflect their sense of self (Adler, Hirsch, & Mordaunt, 2006). It is essential that voice and communication specialists be sensitive to individual communication preferences. Communication—style, voice, choice of language, etc.—is personal. Individuals should not be counseled to adopt behaviors with which they are not comfortable or which do not feel authentic. Specialists can best serve their clients by taking the time to understand a person's gender concerns and goals for gender-role expression (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

Individuals may choose the communication behaviors that they wish to acquire in accordance with their gender identity. These decisions are also informed and supported by the knowledge of the voice and communication specialist and by the assessment data for a specific client (Hancock, Krissinger, & Owen, 2010). Assessment includes a client's self-evaluation and a specialist's evaluation of voice, resonance, articulation, spoken language, and non-verbal communication (Adler et al., 2006; Hancock et al., 2010).

Voice-and-communication treatment plans are developed by considering the available research evidence, the clinical knowledge and experience of the specialist, and the client's own goals and values (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia). Targets of treatment typically include pitch, intonation, loudness and stress patterns, voice quality, resonance, articulation, speech rate and phrasing, language, and nonverbal communication (Adler et al., 2006; Davies & Goldberg, 2006; de Bruin, Coerts, & Greven, 2000; Gelfer, 1999; McNeill, 2006; Oates & Dacakis, 1983). Treatment may involve individual and/or group sessions. The frequency and duration of treatment will vary according to a client's needs. Existing protocols for voice-and-communication treatment can be considered in

developing an individualized therapy plan (Carew, Dacakis, & Oates, 2007; Dacakis, 2000; Davies & Goldberg, 2006; Gelfer, 1999; McNeill, Wilson, Clark, & Deakin, 2008; Mount & Salmon, 1988).

Feminizing or masculinizing the voice involves non-habitual use of the voice production mechanism. Prevention measures are necessary to avoid the possibility of vocal misuse and long-term vocal damage. All voice and communication therapy services should therefore include a vocal health component (Adler et al., 2006).

Vocal Health Considerations After Voice Feminization Surgery

As noted in section XI, some transsexual, transgender, and gender-nonconforming people will undergo voice feminization surgery. (Voice deepening can be achieved through masculinizing hormone therapy, but feminizing hormones do not have an impact on the adult MtF voice.) There are varying degrees of satisfaction, safety, and long-term improvement in patients who have had such surgery. It is recommended that individuals undergoing voice feminization surgery also consult a voice and communication specialist to maximize the surgical outcome, help protect vocal health, and learn nonpitch related aspects of communication. Voice surgery procedures should include follow-up sessions with a voice and communication specialist who is licensed and/or credentialed by the board responsible for speech therapists/speech-language pathologists in that country (Kanagalingam et al., 2005; Neumann & Welzel, 2004).

XI

Surgery

Sex Reassignment Surgery Is Effective and Medically Necessary

Surgery – particularly genital surgery – is often the last and the most considered step in the treatment process for gender dysphoria. While many transsexual, transgender, and gender-nonconforming individuals find comfort with their gender identity, role, and expression without surgery, for many others surgery is essential and medically necessary to alleviate their gender dysphoria (Hage & Karim, 2000). For the latter group, relief from gender dysphoria cannot be achieved

without modification of their primary and/or secondary sex characteristics to establish greater congruence with their gender identity. Moreover, surgery can help patients feel more at ease in the presence of sex partners or in venues such as physicians' offices, swimming pools, or health clubs. In some settings, surgery might reduce risk of harm in the event of arrest or search by police or other authorities.

Follow-up studies have shown an undeniable beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective well-being, cosmesis, and sexual function (De Cuypere et al., 2005; Gijs & Brewaeys, 2007; Klein & Gorzalka, 2009; Pfäfflin & Junge, 1998). Additional information on the outcomes of surgical treatments are summarized in Appendix D.

Ethical Questions Regarding Sex Reassignment Surgery

In ordinary surgical practice, pathological tissues are removed to restore disturbed functions, or alterations are made to body features to improve a patient's self image. Some people, including some health professionals, object on ethical grounds to surgery as a treatment for gender dysphoria, because these conditions are thought not to apply.

It is important that health professionals caring for patients with gender dysphoria feel comfortable about altering anatomically normal structures. In order to understand how surgery can alleviate the psychological discomfort and distress of individuals with gender dysphoria, professionals need to listen to these patients discuss their symptoms, dilemmas, and life histories. The resistance against performing surgery on the ethical basis of "above all do no harm" should be respected, discussed, and met with the opportunity to learn from patients themselves about the psychological distress of having gender dysphoria and the potential for harm caused by denying access to appropriate treatments.

Genital and breast/chest surgical treatments for gender dysphoria are not merely another set of elective procedures. Typical elective procedures involve only a private mutually consenting contract between a patient and a surgeon. Genital and breast/chest surgeries as medically necessary treatments for gender dysphoria are to be undertaken only after assessment of the patient by qualified mental health professionals, as outlined in section VII of the SOC. These surgeries may be performed once there is written documentation that this assessment has occurred and that the person has met the criteria for a specific surgical treatment. By following this procedure, mental health professionals, surgeons, and patients share responsibility for the decision to make irreversible changes to the body.

It is unethical to deny availability or eligibility for sex reassignment surgeries solely on the basis of blood seropositivity for blood-borne infections such as HIV or hepatitis C or B.

Relationship of Surgeons with Mental Health Professionals, Hormone-Prescribing Physicians (if Applicable), and Patients (Informed Consent)

The role of a surgeon in the treatment of gender dysphoria is not that of a mere technician. Rather, conscientious surgeons will have insight into each patient's history and the rationale that led to the referral for surgery. To that end, surgeons must talk at length with their patients and have close working relationships with other health professionals who have been actively involved in their clinical care.

Consultation is readily accomplished when a surgeon practices as part of an interdisciplinary health care team. In the absence of this, a surgeon must be confident that the referring mental health professional(s), and if applicable the physician who prescribes hormones, is/are competent in the assessment and treatment of gender dysphoria, because the surgeon is relying heavily on his/her/their expertise.

Once a surgeon is satisfied that the criteria for specific surgeries have been met (as outlined below), surgical treatment should be considered and a preoperative surgical consultation should take place. During this consultation, the procedure and postoperative course should be extensively discussed with the patient. Surgeons are responsible for discussing all of the following with patients seeking surgical treatments for gender dysphoria:

- The different surgical techniques available (with referral to colleagues who provide alternative options);
- The advantages and disadvantages of each technique;
- The limitations of a procedure to achieve “ideal” results; surgeons should provide a full range of before-and-after photographs of their own patients, including both successful and unsuccessful outcomes;
- The inherent risks and possible complications of the various techniques; surgeons should inform patients of their own complication rates with each procedure.

These discussions are the core of the informed consent process, which is both an ethical and legal requirement for any surgical procedure. Ensuring that patients have a realistic expectation of outcomes is important in achieving a result that will alleviate their gender dysphoria.

All of this information should be provided to patients in writing, in a language in which they are fluent, and in graphic illustrations. Patients should receive the information in advance (possibly

via the Internet) and be given ample time to review it carefully. The elements of informed consent should always be discussed face-to-face prior to the surgical intervention. Questions can then be answered and written informed consent can be provided by the patient. Because these surgeries are irreversible, care should be taken to ensure that patients have sufficient time to absorb information fully before they are asked to provide informed consent. A minimum of 24 hours is suggested.

Surgeons should provide immediate aftercare and consultation with other physicians serving the patient in the future. Patients should work with their surgeon to develop an adequate aftercare plan for the surgery.

Overview of Surgical Procedures for the Treatment of Patients with Gender Dysphoria

For the Male-to-Female (MtF) Patient, Surgical Procedures May Include the Following:

1. Breast/chest surgery: augmentation mammoplasty (implants/lipofilling);
2. Genital surgery: penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty;
3. Nongenital, nonbreast surgical interventions: facial feminization surgery, liposuction, lipofilling, voice surgery, thyroid cartilage reduction, gluteal augmentation (implants/lipofilling), hair reconstruction, and various aesthetic procedures.

For the Female-to-Male (FtM) Patient, Surgical Procedures May Include the Following:

1. Breast/chest surgery: subcutaneous mastectomy, creation of a male chest;
2. Genital surgery: hysterectomy/salpingo-oophorectomy, reconstruction of the fixed part of the urethra, which can be combined with a metoidioplasty or with a phalloplasty (employing a pedicled or free vascularized flap), vaginectomy, scrotoplasty, and implantation of erection and/or testicular prostheses;
3. Nongenital, nonbreast surgical interventions: voice surgery (rare), liposuction, lipofilling, pectoral implants, and various aesthetic procedures.

Reconstructive Versus Aesthetic Surgery

The question of whether sex reassignment surgery should be considered “aesthetic” surgery or “reconstructive” surgery is pertinent not only from a philosophical point of view, but also from a financial point of view. Aesthetic or cosmetic surgery is mostly regarded as not medically necessary and therefore is typically paid for entirely by the patient. In contrast, reconstructive procedures are considered medically necessary—with unquestionable therapeutic results—and thus paid for partially or entirely by national health systems or insurance companies.

Unfortunately, in the field of plastic and reconstructive surgery (both in general and specifically for gender-related surgeries), there is no clear distinction between what is purely reconstructive and what is purely cosmetic. Most plastic surgery procedures actually are a mixture of both reconstructive and cosmetic components.

While most professionals agree that genital surgery and mastectomy cannot be considered purely cosmetic, opinions diverge as to what degree other surgical procedures (e.g., breast augmentation, facial feminization surgery) can be considered purely reconstructive. Although it may be much easier to see a phalloplasty or a vaginoplasty as an intervention to end lifelong suffering, for certain patients an intervention like a reduction rhinoplasty can have a radical and permanent effect on their quality of life, and therefore is much more medically necessary than for somebody without gender dysphoria.

Criteria for Surgeries

As for all of the *SOC*, the criteria for initiation of surgical treatments for gender dysphoria were developed to promote optimal patient care. While the *SOC* allow for an individualized approach to best meet a patient's health care needs, a criterion for all breast/chest and genital surgeries is documentation of persistent gender dysphoria by a qualified mental health professional. For some surgeries, additional criteria include preparation and treatment consisting of feminizing/masculinizing hormone therapy and one year of continuous living in a gender role that is congruent with one's gender identity.

These criteria are outlined below. Based on the available evidence and expert clinical consensus, different recommendations are made for different surgeries.

The *SOC* do not specify an order in which different surgeries should occur. The number and sequence of surgical procedures may vary from patient to patient, according to their clinical needs.

Criteria for Breast/Chest Surgery (One Referral)

Criteria for mastectomy and creation of a male chest in FtM patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a prerequisite.

Criteria for breast augmentation (implants/lipofilling) in MtF patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Criteria for Genital Surgery (Two Referrals)

The criteria for genital surgery are specific to the type of surgery being requested.

Criteria for hysterectomy and salpingo-oophorectomy in FtM patients and for orchiectomy in MtF patients:

1. Persistent, well-documented gender dysphoria;

2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled.
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).

The aim of hormone therapy prior to gonadectomy is primarily to introduce a period of reversible estrogen or testosterone suppression, before the patient undergoes irreversible surgical intervention.

These criteria do not apply to patients who are having these procedures for medical indications other than gender dysphoria.

Criteria for metoidioplasty or phalloplasty in FtM patients and for vaginoplasty in MtF patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).
6. 12 continuous months of living in a gender role that is congruent with their gender identity.

Although not an explicit criterion, it is recommended that these patients also have regular visits with a mental health or other medical professional.

Rationale for a preoperative, 12-month experience of living in an identity-congruent gender role:

The criterion noted above for some types of genital surgeries—i.e., that patients engage in 12 continuous months of living in a gender role that is congruent with their gender identity—is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery. As noted in section VII, the social aspects of changing one's gender role are usually challenging—

often more so than the physical aspects. Changing gender role can have profound personal and social consequences, and the decision to do so should include an awareness of what the familial, interpersonal, educational, vocational, economic, and legal challenges are likely to be, so that people can function successfully in their gender role. Support from a qualified mental health professional and from peers can be invaluable in ensuring a successful gender role adaptation (Bockting, 2008).

The duration of 12 months allows for a range of different life experiences and events that may occur throughout the year (e.g., family events, holidays, vacations, season-specific work or school experiences). During this time, patients should present consistently, on a day-to-day basis and across all settings of life, in their desired gender role. This includes coming out to partners, family, friends, and community members (e.g., at school, work, other settings).

Health professionals should clearly document a patient's experience in the gender role in the medical chart, including the start date of living full time for those who are preparing for genital surgery. In some situations, if needed, health professionals may request verification that this criterion has been fulfilled: They may communicate with individuals who have related to the patient in an identity-congruent gender role, or request documentation of a legal name and/or gender marker change, if applicable.

Surgery for People with Psychotic Conditions and Other Serious Mental Illnesses

When patients with gender dysphoria are also diagnosed with severe psychiatric disorders and impaired reality testing (e.g., psychotic episodes, bipolar disorder, dissociative identity disorder, borderline personality disorder), an effort must be made to improve these conditions with psychotropic medications and/or psychotherapy before surgery is contemplated. (Dhejne et al., 2011). Reevaluation by a mental health professional qualified to assess and manage psychotic conditions should be conducted prior to surgery, describing the patient's mental status and readiness for surgery. It is preferable that this mental health professional be familiar with the patient. No surgery should be performed while a patient is actively psychotic (De Cuypere & Vercruysse, 2009).

Competency of Surgeons Performing Breast/Chest or Genital Surgery

Physicians who perform surgical treatments for gender dysphoria should be urologists, gynecologists, plastic surgeons, or general surgeons, and board-certified as such by the relevant national

and/or regional association. Surgeons should have specialized competence in genital reconstructive techniques as indicated by documented supervised training with a more experienced surgeon. Even experienced surgeons must be willing to have their surgical skills reviewed by their peers. An official audit of surgical outcomes and publication of these results would be greatly reassuring to both referring health professionals and patients. Surgeons should regularly attend professional meetings where new techniques are presented. The internet is often effectively used by patients to share information on their experience with surgeons and their teams.

Ideally, surgeons should be knowledgeable about more than one surgical technique for genital reconstruction so that they, in consultation with patients, can choose the ideal technique for each individual. Alternatively, if a surgeon is skilled in a single technique and this procedure is either not suitable for or desired by a patient, the surgeon should inform the patient about other procedures and offer referral to another appropriately skilled surgeon.

Breast/Chest Surgery Techniques and Complications

Although breast/chest appearance is an important secondary sex characteristic, breast presence or size is not involved in the legal definitions of sex and gender and is not necessary for reproduction. The performance of breast/chest operations for treatment of gender dysphoria should be considered with the same care as beginning hormone therapy, as both produce relatively irreversible changes to the body.

For the MtF patient, a breast augmentation (sometimes called “chest reconstruction”) is not different from the procedure in a natal female patient. It is usually performed through implantation of breast prostheses and occasionally with the lipofilling technique. Infections and capsular fibrosis are rare complications of augmentation mammoplasty in MtF patients (Kanhai, Hage, Karim, & Mulder, 1999).

For the FtM patient, a mastectomy or “male chest contouring” procedure is available. For many FtM patients, this is the only surgery undertaken. When the amount of breast tissue removed requires skin removal, a scar will result and the patient should be so informed. Complications of subcutaneous mastectomy can include nipple necrosis, contour irregularities, and unsightly scarring (Monstrey et al., 2008).

Genital Surgery Techniques and Complications

Genital surgical procedures for the MtF patient may include orchiectomy, penectomy, vaginoplasty, clitoroplasty, and labiaplasty. Techniques include penile skin inversion, pedicled colosigmoid

transplant, and free skin grafts to line the neovagina. Sexual sensation is an important objective in vaginoplasty, along with creation of a functional vagina and acceptable cosmesis.

Surgical complications of MtF genital surgery may include complete or partial necrosis of the vagina and labia, fistulas from the bladder or bowel into the vagina, stenosis of the urethra, and vaginas that are either too short or too small for coitus. While the surgical techniques for creating a neovagina are functionally and aesthetically excellent, anorgasmia following the procedure has been reported, and a second stage labiaplasty may be needed for cosmesis (Klein & Gorzalka, 2009; Lawrence, 2006).

Genital surgical procedures for FtM patients may include hysterectomy, salpingo-oophorectomy, vaginectomy, metoidioplasty, scrotoplasty, urethroplasty, placement of testicular prostheses, and phalloplasty. For patients without former abdominal surgery, the laparoscopic technique for hysterectomy and salpingo-oophorectomy is recommended to avoid a lower-abdominal scar. Vaginal access may be difficult as most patients are nulliparous and have often not experienced penetrative intercourse. Current operative techniques for phalloplasty are varied. The choice of techniques may be restricted by anatomical or surgical considerations and by a client's financial considerations. If the objectives of phalloplasty are a neophallus of good appearance, standing micturition, sexual sensation, and/or coital ability, patients should be clearly informed that there are several separate stages of surgery and frequent technical difficulties, which may require additional operations. Even metoidioplasty, which in theory is a one-stage procedure for construction of a microphallus, often requires more than one operation. The objective of standing micturition with this technique can not always be ensured (Monstrey et al., 2009).

Complications of phalloplasty in FtMs may include frequent urinary tract stenoses and fistulas, and occasionally necrosis of the neophallus. Metoidioplasty results in a micropenis, without the capacity for standing urination. Phalloplasty, using a pedicled or a free vascularized flap, is a lengthy, multi-stage procedure with significant morbidity that includes frequent urinary complications and unavoidable donor site scarring. For this reason, many FtM patients never undergo genital surgery other than hysterectomy and salpingo-oophorectomy (Hage & De Graaf, 1993).

Even patients who develop severe surgical complications seldom regret having undergone surgery. The importance of surgery can be appreciated by the repeated finding that quality of surgical results is one of the best predictors of the overall outcome of sex reassignment (Lawrence, 2006).

Other Surgeries

Other surgeries for assisting in body feminization include reduction thyroid chondroplasty (reduction of the Adam's apple), voice modification surgery, suction-assisted lipoplasty (contour

modeling) of the waist, rhinoplasty (nose correction), facial bone reduction, face-lift, and blepharoplasty (rejuvenation of the eyelid). Other surgeries for assisting in body masculinization include liposuction, lipofilling, and pectoral implants. Voice surgery to obtain a deeper voice is rare but may be recommended in some cases, such as when hormone therapy has been ineffective.

Although these surgeries do not require referral by mental health professionals, such professionals can play an important role in assisting clients in making a fully informed decision about the timing and implications of such procedures in the context of the social transition.

Although most of these procedures are generally labeled “purely aesthetic,” these same operations in an individual with severe gender dysphoria can be considered medically necessary, depending on the unique clinical situation of a given patient’s condition and life situation. This ambiguity reflects reality in clinical situations, and allows for individual decisions as to the need and desirability of these procedures.

XII

Postoperative Care and Follow-Up

Long-term postoperative care and follow-up after surgical treatments for gender dysphoria are associated with good surgical and psychosocial outcomes (Monstrey et al., 2009). Follow-up is important to a patient’s subsequent physical and mental health and to a surgeon’s knowledge about the benefits and limitations of surgery. Surgeons who operate on patients coming from long distances should include personal follow-up in their care plan and attempt to ensure affordable local long-term aftercare in their patients’ geographic region.

Postoperative patients may sometimes exclude themselves from follow-up by specialty providers, including the hormone-prescribing physician (for patients receiving hormones), not recognizing that these providers are often best able to prevent, diagnose, and treat medical conditions that are unique to hormonally and surgically treated patients. The need for follow-up equally extends to mental health professionals, who may have spent a longer period of time with the patient than any other professional and therefore are in an excellent position to assist in any postoperative adjustment difficulties. Health professionals should stress the importance of postoperative follow-up care with their patients and offer continuity of care.

Postoperative patients should undergo regular medical screening according to recommended guidelines for their age. This is discussed more in the next section.

XIII

Lifelong Preventive and Primary Care

Transsexual, transgender, and gender-nonconforming people need health care throughout their lives. For example, to avoid the negative secondary effects of having a gonadectomy at a relatively young age and/or receiving long-term, high-dose hormone therapy, patients need thorough medical care by providers experienced in primary care and transgender health. If one provider is not able to provide all services, ongoing communication among providers is essential.

Primary care and health maintenance issues should be addressed before, during, and after any possible changes in gender role and medical interventions to alleviate gender dysphoria. While hormone providers and surgeons play important roles in preventive care, every transsexual, transgender, and gender-nonconforming person should partner with a primary care provider for overall health care needs (Feldman, 2007).

General Preventive Health Care

Screening guidelines developed for the general population are appropriate for organ systems that are unlikely to be affected by feminizing/masculinizing hormone therapy. However, in areas such as cardiovascular risk factors, osteoporosis, and some cancers (breast, cervical, ovarian, uterine, and prostate), such general guidelines may either over- or underestimate the cost-effectiveness of screening individuals who are receiving hormone therapy.

Several resources provide detailed protocols for the primary care of patients undergoing feminizing/masculinizing hormone therapy, including therapy that is provided after sex reassignment surgeries (Center of Excellence for Transgender Health, UCSF, 2011; Feldman & Goldberg, 2006; Feldman, 2007; Gorton, Buth, & Spade, 2005). Clinicians should consult their national evidence-based guidelines and discuss screening with their patients in light of the effects of hormone therapy on their baseline risk.

Cancer Screening

Cancer screening of organ systems that are associated with sex can present particular medical and psychosocial challenges for transsexual, transgender, and gender-nonconforming patients and their health care providers. In the absence of large-scale prospective studies, providers are unlikely to have enough evidence to determine the appropriate type and frequency of cancer screenings for this population. Over-screening results in higher health care costs, high false positive rates, and often unnecessary exposure to radiation and/or diagnostic interventions such as biopsies. Under-screening results in diagnostic delay for potentially treatable cancers. Patients may find cancer screening gender affirming (such as mammograms for MtF patients) or both physically and emotionally painful (such as Pap smears offer continuity of care for FtM patients).

Urogenital Care

Gynecologic care may be necessary for transsexual, transgender, and gender-nonconforming people of both sexes. For FtM patients, such care is needed predominantly for individuals who have not had genital surgery. For MtF patients, such care is needed after genital surgery. While many surgeons counsel patients regarding postoperative urogenital care, primary care clinicians and gynecologists should also be familiar with the special genital concerns of this population.

All MtF patients should receive counseling regarding genital hygiene, sexuality, and prevention of sexually transmitted infections; those who have had genital surgery should also be counseled on the need for regular vaginal dilation or penetrative intercourse in order to maintain vaginal depth and width (van Trotsenburg, 2009). Due to the anatomy of the male pelvis, the axis and the dimensions of the neovagina differ substantially from those of a biologic vagina. This anatomic difference can affect intercourse if not understood by MtF patients and their partners (van Trotsenburg, 2009).

Lower urinary tract infections occur frequently in MtF patients who have had surgery because of the reconstructive requirements of the shortened urethra. In addition, these patients may suffer from functional disorders of the lower urinary tract; such disorders may be caused by damage of the autonomous nerve supply of the bladder floor during dissection between the rectum and the bladder, and by a change of the position of the bladder itself. A dysfunctional bladder (e.g., overactive bladder, stress or urge urinary incontinence) may occur after sex reassignment surgery (Hoebeker et al., 2005; Kuhn, Hildebrand, & Birkhauser, 2007).

Most FtM patients do not undergo vaginectomy (colpectomy). For patients who take masculinizing hormones, despite considerable conversion of testosterone to estrogens, atrophic changes of the vaginal lining can be observed regularly and may lead to pruritus or burning. Examination can be

both physically and emotionally painful, but lack of treatment can seriously aggravate the situation. Gynecologists treating the genital complaints of FtM patients should be aware of the sensitivity that patients with a male gender identity and masculine gender expression might have around having genitals typically associated with the female sex.

XIV

Applicability of the *Standards of Care* to People Living in Institutional Environments

The SOC in their entirety apply to all transsexual, transgender, and gender-nonconforming people, irrespective of their housing situation. People should not be discriminated against in their access to appropriate health care based on where they live, including institutional environments such as prisons or long-/intermediate-term health care facilities (Brown, 2009). Health care for transsexual, transgender, and gender-nonconforming people living in an institutional environment should mirror that which would be available to them if they were living in a non-institutional setting within the same community.

All elements of assessment and treatment as described in the SOC can be provided to people living in institutions (Brown, 2009). Access to these medically necessary treatments should not be denied on the basis of institutionalization or housing arrangements. If the in-house expertise of health professionals in the direct or indirect employ of the institution does not exist to assess and/or treat people with gender dysphoria, it is appropriate to obtain outside consultation from professionals who are knowledgeable about this specialized area of health care.

People with gender dysphoria in institutions may also have coexisting mental health conditions (Cole et al., 1997). These conditions should be evaluated and treated appropriately.

People who enter an institution on an appropriate regimen of hormone therapy should be continued on the same, or similar, therapies and monitored according to the SOC. A “freeze frame” approach is not considered appropriate care in most situations (*Kosilek v. Massachusetts Department of Corrections/Maloney*, C.A. No. 92–12820-MLW, 2002). People with gender dysphoria who are deemed appropriate for hormone therapy (following the SOC) should be started on such therapy. The consequences of abrupt withdrawal of hormones or lack of initiation of hormone therapy when medically necessary include a high likelihood of negative outcomes such as surgical self-treatment by autocastration, depressed mood, dysphoria, and/or suicidality (Brown, 2010).

Reasonable accommodations to the institutional environment can be made in the delivery of care consistent with the SOC, if such accommodations do not jeopardize the delivery of medically necessary care to people with gender dysphoria. An example of a reasonable accommodation is the use of injectable hormones, if not medically contraindicated, in an environment where diversion of oral preparations is highly likely (Brown, 2009). Denial of needed changes in gender role or access to treatments, including sex reassignment surgery, on the basis of residence in an institution are not reasonable accommodations under the SOC (Brown, 2010).

Housing and shower/bathroom facilities for transsexual, transgender, and gender-nonconforming people living in institutions should take into account their gender identity and role, physical status, dignity, and personal safety. Placement in a single-sex housing unit, ward, or pod on the sole basis of the appearance of the external genitalia may not be appropriate and may place the individual at risk for victimization (Brown, 2009).

Institutions where transsexual, transgender, and gender-nonconforming people reside and receive health care should monitor for a tolerant and positive climate to ensure that residents are not under attack by staff or other residents.

XV

Applicability of the *Standards of Care* to People With Disorders of Sex Development

Terminology

The term *disorder of sex development* (DSD) refers to a somatic condition of atypical development of the reproductive tract (Hughes, Houk, Ahmed, Lee, & LWPES/ESPE Consensus Group, 2006). DSDs include the condition that used to be called *intersexuality*. Although the terminology was changed to DSD during an international consensus conference in 2005 (Hughes et al., 2006), disagreement about language use remains. Some people object strongly to the “disorder” label, preferring instead to view these congenital conditions as a matter of diversity (Diamond, 2009) and to continue using the terms *intersex* or *intersexuality*. In the SOC, WPATH uses the term DSD in an objective and value-free manner, with the goal of ensuring that health professionals recognize this medical term and use it to access relevant literature as the field progresses. WPATH remains

open to new terminology that will further illuminate the experience of members of this diverse population and lead to improvements in health care access and delivery.

Rationale for Addition to the SOC

Previously, individuals with a DSD who also met the *DSM-IV-TR*'s behavioral criteria for Gender Identity Disorder (American Psychiatric Association, 2000) were excluded from that general diagnosis. Instead, they were categorized as having a "Gender Identity Disorder - Not Otherwise Specified." They were also excluded from the WPATH *Standards of Care*.

The current proposal for *DSM-5* (www.dsm5.org) is to replace the term *gender identity disorder* with *gender dysphoria*. Moreover, the proposed changes to the *DSM* consider gender dysphoric people with a DSD to have a subtype of gender dysphoria. This proposed categorization—which explicitly differentiates between gender dysphoric individuals with and without a DSD—is justified: In people with a DSD, gender dysphoria differs in its phenomenological presentation, epidemiology, life trajectories, and etiology (Meyer-Bahlburg, 2009).

Adults with a DSD and gender dysphoria have increasingly come to the attention of health professionals. Accordingly, a brief discussion of their care is included in this version of the SOC.

Health History Considerations

Health professionals assisting patients with both a DSD and gender dysphoria need to be aware that the medical context in which such patients have grown up is typically very different from that of people without a DSD.

Some people are recognized as having a DSD through the observation of gender-atypical genitals at birth. (Increasingly this observation is made during the prenatal period by way of imaging procedures such as ultrasound.) These infants then undergo extensive medical diagnostic procedures. After consultation among the family and health professionals—during which the specific diagnosis, physical and hormonal findings, and feedback from long-term outcome studies (Cohen-Kettenis, 2005; Dessens, Slijper, & Drop, 2005; Jurgensen, Hiort, Holterhus, & Thyen, 2007; Mazur, 2005; Meyer-Bahlburg, 2005; Stikkelbroeck et al., 2003; Wisniewski, Migeon, Malouf, & Gearhart, 2004) are considered—the newborn is assigned a sex, either male or female.

Other individuals with a DSD come to the attention of health professionals around the age of puberty through the observation of atypical development of secondary sex characteristics. This observation also leads to a specific medical evaluation.

The type of DSD and severity of the condition has significant implications for decisions about a patient's initial sex assignment, subsequent genital surgery, and other medical and psychosocial care (Meyer-Bahlburg, 2009). For instance, the degree of prenatal androgen exposure in individuals with a DSD has been correlated with the degree of masculinization of gender-related *behavior* (that is, *gender role and expression*); however, the correlation is only moderate, and considerable behavioral variability remains unaccounted for by prenatal androgen exposure (Jurgensen et al., 2007; Meyer-Bahlburg, Dolezal, Baker, Ehrhardt, & New, 2006). Notably, a similar correlation of prenatal hormone exposure with gender *identity* has not been demonstrated (e.g., Meyer-Bahlburg et al., 2004). This is underlined by the fact that people with the same (core) gender identity can vary widely in the degree of masculinization of their gender-related behavior.

Assessment and Treatment of Gender Dysphoria in People with Disorders of Sex Development

Very rarely are individuals with a DSD identified as having gender dysphoria *before* a DSD diagnosis has been made. Even so, a DSD diagnosis is typically apparent with an appropriate history and basic physical exam—both of which are part of a medical evaluation for the appropriateness of hormone therapy or surgical interventions for gender dysphoria. Mental health professionals should ask their clients presenting with gender dysphoria to have a physical exam, particularly if they are not currently seeing a primary care (or other health care) provider.

Most people with a DSD who are born with genital ambiguity do not develop gender dysphoria (e.g., Meyer-Bahlburg, Dolezal, et al., 2004; Wisniewski et al., 2004). However, some people with a DSD will develop chronic gender dysphoria and even undergo a change in their birth-assigned sex and/or their gender role (Meyer-Bahlburg, 2005; Wilson, 1999; Zucker, 1999). If there are persistent and strong indications that gender dysphoria is present, a comprehensive evaluation by clinicians skilled in the assessment and treatment of gender dysphoria is essential, irrespective of the patient's age. Detailed recommendations have been published for conducting such an assessment and for making treatment decisions to address gender dysphoria in the context of a DSD (Meyer-Bahlburg, 2011). Only after thorough assessment should steps be taken in the direction of changing a patient's birth-assigned sex or gender role.

Clinicians assisting these patients with treatment options to alleviate gender dysphoria may profit from the insights gained from providing care to patients without a DSD (Cohen-Kettenis, 2010).

However, certain criteria for treatment (e.g., age, duration of experience with living in the desired gender role) are usually not routinely applied to people with a DSD; rather, the criteria are interpreted in light of a patient's specific situation (Meyer-Bahlburg, 2011). In the context of a DSD, changes in birth-assigned sex and gender role have been made at any age between early elementary-school age and middle adulthood. Even genital surgery may be performed much earlier in these patients than in gender dysphoric individuals without a DSD if the surgery is well justified by the diagnosis, by the evidence-based gender-identity prognosis for the given syndrome and syndrome severity, and by the patient's wishes.

One reason for these treatment differences is that genital surgery in individuals with a DSD is quite common in infancy and adolescence. Infertility may already be present due to either early gonadal failure or to gonadectomy because of a malignancy risk. Even so, it is advisable for patients with a DSD to undergo a full social transition to another gender role only if there is a long-standing history of gender-atypical behavior, and if gender dysphoria and/or the desire to change one's gender role has been strong and persistent for a considerable period of time. Six months is the time period of full symptom expression required for the application of the gender dysphoria diagnosis proposed for *DSM-5* (Meyer-Bahlburg, 2011).

Additional Resources

The gender-relevant medical histories of people with a DSD are often complex. Their histories may include a great variety of inborn genetic, endocrine, and somatic atypicalities, as well as various hormonal, surgical, and other medical treatments. For this reason, many additional issues need to be considered in the psychosocial and medical care of such patients, regardless of the presence of gender dysphoria. Consideration of these issues is beyond what can be covered in the SOC. The interested reader is referred to existing publications (e.g., Cohen-Kettenis & Pfäfflin, 2003; Meyer-Bahlburg, 2002, 2008). Some families and patients also find it useful to consult or work with community support groups.

There is a very substantial medical literature on the medical management of patients with a DSD. Much of this literature has been produced by high-level specialists in pediatric endocrinology and urology, with input from specialized mental health professionals, especially in the area of gender. Recent international consensus conferences have addressed evidence-based care guidelines (including issues of gender and of genital surgery) for DSD in general (Hughes et al., 2006) and specifically for Congenital Adrenal Hyperplasia (Joint LWPES/ESPE CAH Working Group et al., 2002; Speiser et al., 2010). Others have addressed the research needs for DSD in general (Meyer-Bahlburg & Blizzard, 2004) and for selected syndromes such as 46,XXY (Simpson et al., 2003).



References

- Abramowitz, S. I. (1986). Psychosocial outcomes of sex reassignment surgery. *Journal of Consulting and Clinical Psychology*, 54(2), 183–189. doi:10.1037/0022-006X.54.2.183
- ACOG Committee of Gynecologic Practice. (2005). Committee opinion #322: Compounded bioidentical hormones. *Obstetrics & Gynecology*, 106(5), 139–140.
- Adler, R. K., Hirsch, S., & Mordaunt, M. (2006). *Voice and communication therapy for the transgender/transsexual client: A comprehensive clinical guide*. San Diego, CA: Plural Pub.
- American Academy of Family Physicians. (2005). *Definition of family medicine*. Retrieved from <http://www.aafp.org/online/en/home/policy/policies/f/fammeddef.html>
- American Medical Association. (2008). *Resolution 122 (A-08)*. Retrieved from <http://www.ama-assn.org/ama1/pub/upload/mm/471/122.doc>
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders DSM-IV-TR* (4th ed., text rev.). Washington, DC: Author.
- American Speech-Language-Hearing Association. (2011). *Scope of practice*. Retrieved from www.asha.org
- Anton, B. S. (2009). Proceedings of the American Psychological Association for the legislative year 2008: Minutes of the annual meeting of the council of representatives, February 22–24, 2008, Washington, DC, and August 13 and 17, 2008, Boston, MA, and minutes of the February, June, August, and December 2008 meetings of the board of directors. *American Psychologist*, 64, 372–453. doi:10.1037/a0015932
- Asscheman, H., Giltay, E. J., Megens, J. A. J., de Ronde, W., van Trotsenburg, M. A. A., & Gooren, L. J. G. (2011). A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *European Journal of Endocrinology*, 164(4), 635–642. doi:10.1530/EJE-10-1038
- Baba, T., Endo, T., Honnma, H., Kitajima, Y., Hayashi, T., Ikeda, H., . . . Saito, T. (2007). Association between polycystic ovary syndrome and female-to-male transsexuality. *Human Reproduction*, 22(4), 1011–1016. doi:10.1093/humrep/del474

- Bakker, A., Van Kesteren, P. J., Gooren, L. J., & Bezemer, P. D. (1993). The prevalence of transsexualism in the Netherlands. *Acta Psychiatrica Scandinavica*, 87(4), 237–238. doi:10.1111/j.1600-0447.1993.tb03364.x
- Balen, A. H., Schachter, M. E., Montgomery, D., Reid, R. W., & Jacobs, H. S. (1993). Polycystic ovaries are a common finding in untreated female to male transsexuals. *Clinical Endocrinology*, 38(3), 325–329. doi:10.1111/j.1365-2265.1993.tb01013.x
- Basson, R. (2001). Towards optimal hormonal treatment of male to female gender identity disorder. *Journal of Sexual and Reproductive Medicine*, 1(1), 45–51.
- Basson, R., & Prior, J. C. (1998). Hormonal therapy of gender dysphoria: The male-to-female transsexual. In D. Denny (Ed.), *Current concepts in transgender identity* (pp. 277–296). New York, NY: Garland.
- Benjamin, H. (1966). *The transsexual phenomenon*. New York, NY: Julian Press.
- Besnier, N. (1994). Polynesian gender liminality through time and space. In G. Herdt (Ed.), *Third sex, third gender: Beyond sexual dimorphism in culture and history* (pp. 285–328). New York: Zone Books.
- Bockting, W. O. (1999). From construction to context: Gender through the eyes of the transgendered. *Siecus Report*, 28(1), 3–7.
- Bockting, W. O. (2008). Psychotherapy and the real-life experience: From gender dichotomy to gender diversity. *Sexologies*, 17(4), 211–224. doi:10.1016/j.sexol.2008.08.001
- Bockting, W. O., & Coleman, E. (2007). Developmental stages of the transgender coming out process: Toward an integrated identity. In R. Ettner, S. Monstrey & A. Eyler (Eds.), *Principles of transgender medicine and surgery* (pp. 185–208). New York, NY: The Haworth Press.
- Bockting, W. O., & Goldberg, J. M. (2006). Guidelines for transgender care (Special issue). *International Journal of Transgenderism*, 9(3/4).
- Bockting, W. O., Knudson, G., & Goldberg, J. M. (2006). Counseling and mental health care for transgender adults and loved ones. *International Journal of Transgenderism*, 9(3/4), 35–82. doi:10.1300/J485v09n03_03
- Bolin, A. (1988). *In search of Eve* (pp. 189–192). New York, NY: Bergin & Garvey.
- Bolin, A. (1994). Transcending and transgendering: Male-to-female transsexuals, dichotomy and diversity. In G. Herdt (Ed.), *Third sex, third gender: Beyond sexual dimorphism in culture and history* (pp. 447–486). New York, NY: Zone Books.
- Bornstein, K. (1994). *Gender outlaw: On men, women, and the rest of us*. New York, NY: Routledge.

- Bosinski, H. A. G., Peter, M., Bonatz, G., Arndt, R., Heidenreich, M., Sippell, W. G., & Wille, R. (1997). A higher rate of hyperandrogenic disorders in female-to-male transsexuals. *Psychoneuroendocrinology*, 22(5), 361–380. doi:10.1016/S0306-4530(97)00033-4
- Brill, S. A., & Pepper, R. (2008). *The transgender child: A handbook for families and professionals*. Berkeley, CA: Cleis Press.
- Brown, G. R. (2009). Recommended revisions to The World Professional Association for Transgender Health's *Standards of Care* section on medical care for incarcerated persons with gender identity disorder. *International Journal of Transgenderism*, 11(2), 133–139. doi:10.1080/15532730903008073
- Brown, G. R. (2010). Autocastration and autopenectomy as surgical self-treatment in incarcerated persons with gender identity disorder. *International Journal of Transgenderism*, 12(1), 31–39. doi:10.1080/15532731003688970
- Bullough, V. L., & Bullough, B. (1993). *Cross dressing, sex, and gender*. Philadelphia, PA: University of Pennsylvania Press.
- Callen Lorde Community Health Center. (2000). *Transgender health program protocols*. Retrieved from http://www.callen-lorde.org/documents/TG_Protocol_Request_Form2.pdf
- Callen Lorde Community Health Center. (2011). *Transgender health program protocols*. Retrieved from http://www.callen-lorde.org/documents/TG_Protocol_Request_Form2.pdf
- Canadian Association of Speech-Language Pathologists and Audiologists. (n.d.). CASLPA *clinical certification program*. Retrieved from <http://www.caslpa.ca/>
- Carew, L., Dacakis, G., & Oates, J. (2007). The effectiveness of oral resonance therapy on the perception of femininity of voice in male-to-female transsexuals. *Journal of Voice*, 21(5), 591–603. doi:10.1016/j.jvoice.2006.05.005
- Carnegie, C. (2004). Diagnosis of hypogonadism: Clinical assessments and laboratory tests. *Reviews in Urology*, 6(Suppl 6), S3–8.
- Cattrall, F. R., & Healy, D. L. (2004). Long-term metabolic, cardiovascular and neoplastic risks with polycystic ovary syndrome. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 18(5), 803–812. doi:10.1016/j.bpobgyn.2004.05.005
- Center of Excellence for Transgender Health, UCSF. (2011). *Primary care protocol for transgender health care*. Retrieved from <http://transhealth.ucsf.edu/trans?page=protocol-00-00>
- Chiñas, B. (1995). Isthmus Zapotec attitudes toward sex and gender anomalies. In S. O. Murray (Ed.), *Latin American male homosexualities* (pp. 293–302). Albuquerque, NM: University of New Mexico Press.

- Clements, K., Wilkinson, W., Kitano, K., & Marx, R. (1999). HIV prevention and health service needs of the transgender community in San Francisco. *International Journal of Transgenderism*, 3(1), 2–17.
- Cohen-Kettenis, P. T. (2001). Gender identity disorder in DSM? *Journal of the American Academy of Child & Adolescent Psychiatry*, 40(4), 391–391. doi:10.1097/00004583-200104000-00006
- Cohen-Kettenis, P. T. (2005). Gender change in 46,XY persons with 5 α -reductase-2 deficiency and 17 β -hydroxysteroid dehydrogenase-3 deficiency. *Archives of Sexual Behavior*, 34(4), 399–410. doi:10.1007/s10508-005-4339-4
- Cohen-Kettenis, P. T. (2006). Gender identity disorders. In C. Gillberg, R. Harrington & H. C. Steinhausen (Eds.), *A clinician's handbook of child and adolescent psychiatry* (pp. 695–725). New York, NY: Cambridge University Press.
- Cohen-Kettenis, P. T. (2010). Psychosocial and psychosexual aspects of disorders of sex development. *Best Practice & Research Clinical Endocrinology & Metabolism*, 24(2), 325–334. doi:10.1016/j.beem.2009.11.005
- Cohen-Kettenis, P. T., & Kuiper, A. J. (1984). Transseksualiteit en psychotherapie. *Tijdschrift Voor Psychotherapie*, 10, 153–166.
- Cohen-Kettenis, P. T., Owen, A., Kaijser, V. G., Bradley, S. J., & Zucker, K. J. (2003). Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: A cross-national, cross-clinic comparative analysis. *Journal of Abnormal Child Psychology*, 31(1), 41–53. doi:10.1023/A:1021769215342
- Cohen-Kettenis, P. T., & Pfäfflin, F. (2003). *Transgenderism and intersexuality in childhood and adolescence: Making choices*. Thousand Oaks, CA: Sage.
- Cohen-Kettenis, P. T., & Pfäfflin, F. (2010). The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Archives of Sexual Behavior*, 39(2), 499–513. doi:10.1007/s10508-009-9562-y
- Cohen-Kettenis, P. T., Schagen, S. E. E., Steensma, T. D., de Vries, A. L. C., & Delemarre-van de Waal, H. A. (2011). Puberty suppression in a gender-dysphoric adolescent: A 22-year follow-up. *Archives of Sexual Behavior*, 40(4), 843–847. doi:10.1007/s10508-011-9758-9
- Cohen-Kettenis, P. T., Wallien, M., Johnson, L. L., Owen-Anderson, A. F. H., Bradley, S. J., & Zucker, K. J. (2006). A parent-report gender identity questionnaire for children: A cross-national, cross-clinic comparative analysis. *Clinical Child Psychology and Psychiatry*, 11(3), 397–405. doi:10.1177/1359104506059135

- Cole, C. M., O'Boyle, M., Emory, L. E., & Meyer III, W. J. (1997). Comorbidity of gender dysphoria and other major psychiatric diagnoses. *Archives of Sexual Behavior*, 26(1), 13–26.
- Coleman, E. (2009a). Toward version 7 of the World Professional Association for Transgender Health's *Standards of Care*. *International Journal of Transgenderism*, 11(1), 1–7. doi: 10.1080/15532730902799912
- Coleman, E. (2009b). Toward version 7 of the World Professional Association for Transgender Health's *Standards of Care*: Psychological assessment and approaches to treatment. *International Journal of Transgenderism*, 11(2), 69–73. doi: 10.1080/15532730903008008
- Coleman, E. (2009c). Toward version 7 of the World Professional Association for Transgender Health's *Standards of Care*: Hormonal and surgical approaches to treatment. *International Journal of Transgenderism*, 11(3), 141–145. doi: 10.1080/15532730903383740
- Coleman, E. (2009d). Toward version 7 of the World Professional Association for Transgender Health's *Standards of Care*: Medical and therapeutic approaches to treatment. *International Journal of Transgenderism*, 11(4), 215–219. doi: 10.1080/15532730903439450
- Coleman, E., Colgan, P., & Gooren, L. (1992). Male cross-gender behavior in Myanmar (Burma): A description of the acault. *Archives of Sexual Behavior*, 21(3), 313–321.
- Costa, L. M., & Matzner, A. (2007). *Male bodies, women's souls: Personal narratives of Thailand's transgendered youth*. Binghamton, NY: Haworth Press.
- Currah, P., Juang, R. M., & Minter, S. (2006). *Transgender rights*. Minneapolis, MN: University of Minnesota Press.
- Currah, P., & Minter, S. (2000). Unprincipled exclusions: The struggle to achieve judicial and legislative equality for transgender people. *William and Mary Journal of Women and Law*, 7, 37–60.
- Dacakis, G. (2000). Long-term maintenance of fundamental frequency increases in male-to-female transsexuals. *Journal of Voice*, 14(4), 549–556. doi:10.1016/S0892–1997(00)80010–7
- Dahl, M., Feldman, J. L., Goldberg, J. M., & Jaber, A. (2006). Physical aspects of transgender endocrine therapy. *International Journal of Transgenderism*, 9(3), 111–134. doi:10.1300/J485v09n03_06
- Darney, P. D. (2008). Hormonal contraception. In H. M. Kronenberg, S. Melmer, K. S. Polonsky & P. R. Larsen (Eds.), *Williams textbook of endocrinology* (11th ed., pp. 615–644). Philadelphia: Saunders.
- Davies, S., & Goldberg, J. M. (2006). Clinical aspects of transgender speech feminization and masculinization. *International Journal of Transgenderism*, 9(3–4), 167–196. doi:10.1300/J485v09n03_08

- de Bruin, M. D., Coerts, M. J., & Greven, A. J. (2000). Speech therapy in the management of male-to-female transsexuals. *Folia Phoniatica Et Logopaedica*, 52(5), 220–227.
- De Cuypere, G., T'Sjoen, G., Beerten, R., Selvaggi, G., De Sutter, P., Hoebeke, P., . . . Rubens, R. (2005). Sexual and physical health after sex reassignment surgery. *Archives of Sexual Behavior*, 34(6), 679–690. doi:10.1007/s10508-005-7926-5
- De Cuypere, G., Van Hemelrijck, M., Michel, A., Carael, B., Heylens, G., Rubens, R., . . . Monstrey, S. (2007). Prevalence and demography of transsexualism in Belgium. *European Psychiatry*, 22(3), 137–141. doi:10.1016/j.eurpsy.2006.10.002
- De Cuypere, G., & Vercruysse, H. (2009). Eligibility and readiness criteria for sex reassignment surgery: Recommendations for revision of the WPATH standards of care. *International Journal of Transgenderism*, 11(3), 194–205. doi:10.1080/15532730903383781
- Delemarre-van de Waal, H. A., & Cohen-Kettenis, P. T. (2006). Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspects. *European Journal of Endocrinology*, 155(Suppl 1), S131–S137. doi:10.1530/eje.1.02231
- Delemarre-van de Waal, H. A., van Weissenbruch, M. M., & Cohen Kettenis, P. T. (2004). Management of puberty in transsexual boys and girls. *Hormone Research in Paediatrics*, 62(Suppl 2), 75–75. doi:10.1159/000081145
- de Lignières, B. (1999). Oral micronized progesterone. *Clinical Therapeutics*, 21(1), 41–60. doi:10.1016/S0149-2918(00)88267-3
- Derrig-Palumbo, K., & Zeine, F. (2005). *Online therapy: A therapist's guide to expanding your practice*. New York, NY: W.W. Norton.
- Dessens, A. B., Slijper, F. M. E., & Drop, S. L. S. (2005). Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Archives of Sexual Behavior*, 34(4), 389–397. doi:10.1007/s10508-005-4338-5
- De Sutter, P. (2009). Reproductive options for transpeople: Recommendations for revision of the WPATH's standards of care. *International Journal of Transgenderism*, 11(3), 183–185. doi:10.1080/15532730903383765
- De Sutter, P., Kira, K., Verschoor, A., & Hotimsky, A. (2002). The desire to have children and the preservation of fertility in transsexual women: A survey. *International Journal of Transgenderism*, 6(3), retrieved from http://www.wpath.org/journal/www.iiav.nl/ezines/web/IJT/97-03/numbers/symposion/ijtvo06no03_02.htm
- Devor, A. H. (2004). Witnessing and mirroring: A fourteen stage model. *Journal of Gay and Lesbian Psychotherapy*, 8(1/2), 41–67.
- de Vries, A. L. C., Cohen-Kettenis, P. T., & Delemarre-van de Waal, H. A. (2006). Clinical management of gender dysphoria in adolescents. *International Journal of Transgenderism*, 9(3–4), 83–94. doi:10.1300/J485v09n03_04

- de Vries, A. L. C., Doreleijers, T. A. H., Steensma, T. D., & Cohen-Kettenis, P. T. (2011). Psychiatric comorbidity in gender dysphoric adolescents. *Journal of Child Psychology and Psychiatry*. Advance online publication. doi:10.1111/j.1469-7610.2011.02426.x
- de Vries, A. L. C., Noens, I. L. J., Cohen-Kettenis, P. T., van Berckelaer-Onnes, I. A., & Doreleijers, T. A. (2010). Autism spectrum disorders in gender dysphoric children and adolescents. *Journal of Autism and Developmental Disorders*, 40(8), 930–936. doi:10.1007/s10803-010-0935-9
- de Vries, A. L. C., Steensma, T. D., Doreleijers, T. A. H., & Cohen-Kettenis, P. T. (2010). Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. *The Journal of Sexual Medicine*. Advance online publication. doi:10.1111/j.1743-6109.2010.01943.x
- Dhejne, C., Lichtenstein, P., Boman, M., Johansson, A. L. V., Langstrom, N., & Landen, M. (2011). Longterm follow-up of transsexual persons undergoing sex reassignment surgery: Cohort study in Sweden. *PloS ONE*, 6(2), 1–8. doi:10.1371/journal.pone.0016885
- Diamond, M. (2009). Human intersexuality: Difference or disorder? *Archives of Sexual Behavior*, 38(2), 172–172. doi:10.1007/s10508-008-9438-6
- Di Ceglie, D., & Thümmel, E. C. (2006). An experience of group work with parents of children and adolescents with gender identity disorder. *Clinical Child Psychology and Psychiatry*, 11(3), 387–396. doi:10.1177/1359104506064983
- Dobs, A. S., Meikle, A. W., Arver, S., Sanders, S. W., Caramelli, K. E., & Mazer, N. A. (1999). Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *Journal of Clinical Endocrinology & Metabolism*, 84(10), 3469–3478. doi:10.1210/jc.84.10.3469
- Docter, R. F. (1988). *Transvestites and transsexuals: Toward a theory of cross-gender behavior*. New York, NY: Plenum Press.
- Drummond, K. D., Bradley, S. J., Peterson-Badali, M., & Zucker, K. J. (2008). A follow-up study of girls with gender identity disorder. *Developmental Psychology*, 44(1), 34–45. doi:10.1037/0012-1649.44.1.34
- Ehrbar, R. D., & Gorton, R. N. (2010). Exploring provider treatment models in interpreting the *standards of care*. *International Journal of Transgenderism*, 12(4), 198–2010. doi:10.1080/15532739.2010.544235
- Ekins, R., & King, D. (2006). *The transgender phenomenon*. Thousand Oaks, CA: Sage.

- Eklund, P. L., Gooren, L. J., & Bezemer, P. D. (1988). Prevalence of transsexualism in the Netherlands. *British Journal of Psychiatry*, 152(5), 638–640.
- Eldh, J., Berg, A., & Gustafsson, M. (1997). Long-term follow up after sex reassignment surgery. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*, 31(1), 39–45.
- Emerson, S., & Rosenfeld, C. (1996). Stages of adjustment in family members of transgender individuals. *Journal of Family Psychotherapy*, 7(3), 1–12. doi:10.1300/J085V07N03_01
- Emory, L. E., Cole, C. M., Avery, E., Meyer, O., & Meyer III, W. J. (2003). *Client's view of gender identity: Life, treatment status and outcome*. Paper presented at 18th Biennial Harry Benjamin Symposium, Gent, Belgium.
- Ettner, R., Monstrey, S., & Eyler, A. (Eds.) (2007). *Principles of transgender medicine and surgery*. Binghamton, NY: Haworth Press.
- Eyler, A. E. (2007). Primary medical care of the gender-variant patient. In R. Ettner, S. Monstrey & E. Eyler (Eds.), *Principles of transgender medicine and surgery* (pp. 15–32). Binghamton, NY: Haworth Press.
- Factor, R. J., & Rothblum, E. (2008). Exploring gender identity and community among three groups of transgender individuals in the United States: MtFs, FtMs, and genderqueers. *Health Sociology Review*, 17(3), 235–253.
- Feinberg, L. (1996). *Transgender warriors: Making history from Joan of Arc to Dennis Rodman*. Boston, MA: Beacon Press.
- Feldman, J. (2005, April). *Masculinizing hormone therapy with testosterone 1% topical gel*. Paper presented at the 19th Biennial Symposium of the Harry Benjamin International Gender Dysphoria Association, Bologna, Italy.
- Feldman, J. (2007). Preventive care of the transgendered patient. In R. Ettner, S. Monstrey & E. Eyler (Eds.), *Principles of transgender surgery and medicine* (pp. 33–72). Binghamton, NY: Haworth Press.
- Feldman, J., & Goldberg, J. (2006). Transgender primary medical care. *International Journal of Transgenderism*, 9(3), 3–34. doi:10.1300/JJ485v09n03_02
- Feldman, J., & Safer, J. (2009). Hormone therapy in adults: Suggested revisions to the sixth version of the *standards of care*. *International Journal of Transgenderism*, 11(3), 146–182. doi:10.1080/15532730903383757
- Fenichel, M., Suler, J., Barak, A., Zelvin, E., Jones, G., Munro, K., . . . Walker-Schmucker, W. (2004). *Myths and realities of online clinical work, observations on the phenomena of online behavior, experience, and therapeutic relationships. A 3rd-year report from ISMHO's clinical case study group*. Retrieved from https://www.ismho.org/myths_n_realities.asp

- Fenway Community Health Transgender Health Program. (2007). *Protocol for hormone therapy*. Retrieved from http://www.fenwayhealth.org/site/DocServer/Fenway_Protocols.pdf?docID=2181
- Fisk, N. M. (1974). Editorial: Gender dysphoria syndrome—the conceptualization that liberalizes indications for total gender reorientation and implies a broadly based multi-dimensional rehabilitative regimen. *Western Journal of Medicine*, 120(5), 386–391.
- Fitzpatrick, L. A., Pace, C., & Wiita, B. (2000). Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: A cross-sectional survey. *Journal of Women's Health & Gender-Based Medicine*, 9(4), 381–387.
- Frank, J. D., & Frank, J. B. (1993). *Persuasion and healing: A comparative study of psychotherapy* (3rd ed.). Baltimore, MD: Johns Hopkins University Press.
- Fraser, L. (2009a). Depth psychotherapy with transgender people. *Sexual and Relationship Therapy*, 24(2), 126–142. doi:10.1080/14681990903003878
- Fraser, L. (2009b). E-therapy: Ethical and clinical considerations for version 7 of The World Professional Association for Transgender Health's *Standards of Care*. *International Journal of Transgenderism*, 11(4), 247–263. doi:10.1080/15532730903439492
- Fraser, L. (2009c). Psychotherapy in The World Professional Association for Transgender Health's *Standards of Care*: Background and recommendations. *International Journal of Transgenderism*, 11(2), 110–126. doi:10.1080/15532730903008057
- Garaffa, G., Christopher, N. A., & Ralph, D. J. (2010). Total phallic reconstruction in female-to-male transsexuals. *European Urology*, 57(4), 715–722. doi:10.1016/j.eururo.2009.05.018
- Gelder, M. G., & Marks, I. M. (1969). Aversion treatment in transvestism and transsexualism. In R. Green, & J. Money (Eds.), *Transsexualism and sex reassignment* (pp. 383–413). Baltimore, MD: Johns Hopkins University Press.
- Gelfer, M. P. (1999). Voice treatment for the male-to-female transgendered client. *American Journal of Speech-Language Pathology*, 8(3), 201–208.
- Gharib, S., Bigby, J., Chapin, M., Ginsburg, E., Johnson, P., Manson, J., & Solomon, C. (2005). *Menopause: A guide to management*. Boston, MA: Brigham and Women's Hospital.
- Gijs, L., & Brewaeys, A. (2007). Surgical treatment of gender dysphoria in adults and adolescents: Recent developments, effectiveness, and challenges. *Annual Review of Sex Research*, 18, 178–224.

- Gold, M., & MacNish, M. (2011). *Adjustment and resiliency following disclosure of transgender identity in families of adolescents and young adults: Themes and clinical implications*. Washington, DC: American Family Therapy Academy.
- Gómez-Gil, E., Trilla, A., Salamero, M., Godás, T., & Valdés, M. (2009). Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Archives of Sexual Behavior*, 38(3), 378–392. doi:10.1007/s10508-007-9307-8
- Gooren, L. (2005). Hormone treatment of the adult transsexual patient. *Hormone Research in Paediatrics*, 64(Suppl 2), 31–36. doi:10.1159/000087751
- Gorton, R. N., Buth, J., & Spade, D. (2005). *Medical therapy and health maintenance for transgender men: A guide for health care providers*. San Francisco, CA: Lyon-Martin Women's Health Services.
- Green, R. (1987). *The "sissy boy syndrome" and the development of homosexuality*. New Haven, CT: Yale University Press.
- Green, R., & Fleming, D. (1990). Transsexual surgery follow-up: Status in the 1990s. *Annual Review of Sex Research*, 1(1), 163–174.
- Greenson, R. R. (1964). On homosexuality and gender identity. *International Journal of Psycho-Analysis*, 45, 217–219.
- Grossman, A. H., D'Augelli, A. R., Howell, T. J., & Hubbard, S. (2006). Parent's reactions to transgender youth's gender-nonconforming expression and identity. *Journal of Gay & Lesbian Social Services*, 18(1), 3–16. doi:10.1300/J041v18n01_02
- Grossman, A. H., D'Augelli, A. R., & Salter, N. P. (2006). Male-to-female transgender youth: Gender expression milestones, gender atypicality, victimization, and parents' responses. *Journal of GLBT Family Studies*, 2(1), 71–92.
- Grumbach, M. M., Hughes, I. A., & Conte, F. A. (2003). Disorders of sex differentiation. In P. R. Larsen, H. M. Kronenberg, S. Melmed & K. S. Polonsky (Eds.), *Williams textbook of endocrinology* (10th ed., pp. 842–1002). Philadelphia, PA: Saunders.
- Hage, J. J., & De Graaf, F. H. (1993). Addressing the ideal requirements by free flap phalloplasty: Some reflections on refinements of technique. *Microsurgery*, 14(9), 592–598. doi:10.1002/micr.1920140910
- Hage, J. J., & Karim, R. B. (2000). Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plastic and Reconstructive Surgery*, 105(3), 1222–1227.
- Hancock, A. B., Krissinger, J., & Owen, K. (2010). Voice perceptions and quality of life of transgender people. *Journal of Voice*. Advance online publication. doi:10.1016/j.jvoice.2010.07.013

- Hastings, D. W. (1974). Postsurgical adjustment of male transsexual patients. *Clinics in Plastic Surgery*, 1(2), 335–344.
- Hembree, W. C., Cohen-Kettenis, P., Delemarre-van de Waal, H. A., Gooren, L. J., Meyer III, W. J., Spack, N. P., . . . Montori, V. M. (2009). Endocrine treatment of transsexual persons: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, 94(9), 3132–3154. doi:10.1210/jc.2009–0345
- Hill, D. B., Menvielle, E., Sica, K. M., & Johnson, A. (2010). An affirmative intervention for families with gender-variant children: Parental ratings of child mental health and gender. *Journal of Sex and Marital Therapy*, 36(1), 6–23. doi:10.1080/00926230903375560
- Hoebeke, P., Selvaggi, G., Ceulemans, P., De Cuypere, G. D., T'Sjoen, G., Weyers, S., . . . Monstrey, S. (2005). Impact of sex reassignment surgery on lower urinary tract function. *European Urology*, 47(3), 398–402. doi:10.1016/j.eururo.2004.10.008
- Hoenig, J., & Kenna, J. C. (1974). The prevalence of transsexualism in England and Wales. *British Journal of Psychiatry*, 124(579), 181–190. doi:10.1192/bjp.124.2.181
- Hughes, I. A., Houk, C. P., Ahmed, S. F., Lee, P. A., & LWPES/ESPE Consensus Group. (2006). Consensus statement on management of intersex disorders. *Archives of Disease in Childhood*, 91(7), 554–563. doi:10.1136/adc.2006.098319
- Hunter, M. H., & Sterrett, J. J. (2000). Polycystic ovary syndrome: It's not just infertility. *American Family Physician*, 62(5), 1079–1095.
- Institute of Medicine. (2011). *The health of lesbian, gay, bisexual, and transgender people: Building a foundation for better understanding*. Washington, DC: The National Academies Press.
- Jackson, P. A., & Sullivan, G. (Eds.). (1999). *Lady boys, tom boys, rent boys: Male and female homosexualities in contemporary Thailand*. Binghamton, NY: Haworth Press.
- Jockenhövel, F. (2004). Testosterone therapy-what, when and to whom? *The Aging Male*, 7(4), 319–324. doi:10.1080/13685530400016557
- Johansson, A., Sundbom, E., Höjerback, T., & Bodlund, O. (2010). A five-year follow-up study of Swedish adults with gender identity disorder. *Archives of Sexual Behavior*, 39(6), 1429–1437. doi:10.1007/s10508–009–9551–1
- Joint LWPES/ESPE CAH Working Group, Clayton, P. E., Miller, W. L., Oberfield, S. E., Ritzen, E. M., Sippell, W. G., & Speiser, P. W. (2002). Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology. *Journal of Clinical Endocrinology & Metabolism*, 87(9), 4048–4053. doi:10.1210/jc.2002–020611

- Jurgensen, M., Hiort, O., Holterhus, P. M., & Thyen, U. (2007). Gender role behavior in children with XY karyotype and disorders of sex development. *Hormones and Behavior*, 51(3), 443–453. doi:0.1016/j.yhbeh.2007.01.001
- Kanagalingam, J., Georgalas, C., Wood, G. R., Ahluwalia, S., Sandhu, G., & Cheesman, A. D. (2005). Cricothyroid approximation and subluxation in 21 male-to-female transsexuals. *The Laryngoscope*, 115(4), 611–618. doi:10.1097/01.mlg.0000161357.12826.33
- Kanhai, R. C. J., Hage, J. J., Karim, R. B., & Mulder, J. W. (1999). Exceptional presenting conditions and outcome of augmentation mammaplasty in male-to-female transsexuals. *Annals of Plastic Surgery*, 43(5), 476–483.
- Kimberly, S. (1997). I am transsexual - hear me roar. *Minnesota Law & Politics*, June, 21–49.
- Klein, C., & Gorzalka, B. B. (2009). Sexual functioning in transsexuals following hormone therapy and genital surgery: A review (CME). *The Journal of Sexual Medicine*, 6(11), 2922–2939. doi:10.1111/j.1743-6109.2009.01370.x
- Knudson, G., De Cuypere, G., & Bockting, W. (2010a). Process toward consensus on recommendations for revision of the DSM diagnoses of gender identity disorders by The World Professional Association for Transgender Health. *International Journal of Transgenderism*, 12(2), 54–59. doi:10.1080/15532739.2010.509213
- Knudson, G., De Cuypere, G., & Bockting, W. (2010b). Recommendations for revision of the DSM diagnoses of gender identity disorders: Consensus statement of The World Professional Association for Transgender Health. *International Journal of Transgenderism*, 12(2), 115–118. doi:10.1080/15532739.2010.509215
- Kosilek v. Massachusetts Department of Corrections/Maloney, C.A. No. 92–12820-MLW (U.S. Federal District Court, Boston, MA, 2002).
- Krege, S., Bex, A., Lümmen, G., & Rübber, H. (2001). Male-to-female transsexualism: A technique, results and long-term follow-up in 66 patients. *British Journal of Urology*, 88(4), 396–402. doi:10.1046/j.1464-410X.2001.02323.x
- Kuhn, A., Bodmer, C., Stadlmayr, W., Kuhn, P., Mueller, M. D., & Birkhäuser, M. (2009). Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertility and Sterility*, 92(5), 1685–1689. doi:10.1016/j.fertnstert.2008.08.126
- Kuhn, A., Hildebrand, R., & Birkhauser, M. (2007). Do transsexuals have micturition disorders? *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 131(2), 226–230. doi:10.1016/j.ejogrb.2006.03.019
- Landén, M., Wålinder, J., & Lundström, B. (1998). Clinical characteristics of a total cohort of female and male applicants for sex reassignment: A descriptive study. *Acta Psychiatrica Scandinavica*, 97(3), 189–194. doi:10.1111/j.1600-0447.1998.tb09986.x

- Lawrence, A. A. (2003). Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Archives of Sexual Behavior*, 32(4), 299–315. doi:10.1023/A:1024086814364
- Lawrence, A. A. (2006). Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Archives of Sexual Behavior*, 35(6), 717–727. doi:10.1007/s10508-006-9104-9
- Lev, A. I. (2004). *Transgender emergence: Therapeutic guidelines for working with gender-variant people and their families*. Binghamton, NY: Haworth Clinical Practice Press.
- Lev, A. I. (2009). The ten tasks of the mental health provider: Recommendations for revision of The World Professional Association for Transgender Health's standards of care. *International Journal of Transgenderism*, 11(2), 74–99. doi:10.1080/15532730903008032
- Levy, A., Crown, A., & Reid, R. (2003). Endocrine intervention for transsexuals. *Clinical Endocrinology*, 59(4), 409–418. doi:10.1046/j.1365-2265.2003.01821.x
- MacLaughlin, D. T., & Donahoe, P. K. (2004). Sex determination and differentiation. *New England Journal of Medicine*, 350(4), 367–378.
- Maheu, M. M., Pulier, M. L., Wilhelm, F. H., McMenamin, J. P., & Brown-Connolly, N. E. (2005). *The mental health professional and the new technologies: A handbook for practice today*. Mahwah, NJ: Lawrence Erlbaum.
- Malpas, J. (2011). Between pink and blue: A multi-dimensional family approach to gender nonconforming children and their families. *Family Process*, 50(4), 453–470 doi: 10.1111/j.1545-5300.2011.01371.x
- Mazur, T. (2005). Gender dysphoria and gender change in androgen insensitivity or micropenis. *Archives of Sexual Behavior*, 34(4), 411–421. doi:10.1007/s10508-005-4341-x
- McNeill, E. J. M. (2006). Management of the transgender voice. *The Journal of Laryngology & Otology*, 120(07), 521–523. doi:10.1017/S0022215106001174
- McNeill, E. J. M., Wilson, J. A., Clark, S., & Deakin, J. (2008). Perception of voice in the transgender client. *Journal of Voice*, 22(6), 727–733. doi:10.1016/j.jvoice.2006.12.010
- Menvielle, E. J., & Tuerk, C. (2002). A support group for parents of gender-nonconforming boys. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41(8), 1010–1013. doi:10.1097/00004583-200208000-00021
- Meyer, I. H. (2003). Prejudice as stress: Conceptual and measurement problems. *American Journal of Public Health*, 93(2), 262–265.

- Meyer, J. K., & Reter, D. J. (1979). Sex reassignment: Follow-up. *Archives of General Psychiatry*, 36(9), 1010–1015.
- Meyer, W. J. III. (2009). World Professional Association for Transgender Health's *standards of care* requirements of hormone therapy for adults with gender identity disorder. *International Journal of Transgenderism*, 11(2), 127–132. doi:10.1080/155327309033008065
- Meyer, W. J. III. Webb, A., Stuart, C. A., Finkelstein, J. W., Lawrence, B., & Walker, P. A. (1986). Physical and hormonal evaluation of transsexual patients: A longitudinal study. *Archives of Sexual Behavior*, 15(2), 121–138. doi:10.1007/BF01542220
- Meyer-Bahlburg, H. F. L. (2002). Gender assignment and reassignment in intersexuality: Controversies, data, and guidelines for research. *Advances in Experimental Medicine and Biology*, 511, 199–223. doi:10.1007/978-1-4615-0621-8_12
- Meyer-Bahlburg, H. F. L. (2005). Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. *Archives of Sexual Behavior*, 34(4), 423–438. doi:10.1007/s10508-005-4342-9
- Meyer-Bahlburg, H. F. L. (2008). Treatment guidelines for children with disorders of sex development. *Neuropsychiatrie De l'Enfance Et De l'Adolescence*, 56(6), 345–349. doi:10.1016/j.neurenf.2008.06.002
- Meyer-Bahlburg, H. F. L. (2009). Variants of gender differentiation in somatic disorders of sex development. *International Journal of Transgenderism*, 11(4), 226–237. doi:10.1080/15532730903439476
- Meyer-Bahlburg, H. F. L. (2010). From mental disorder to iatrogenic hypogonadism: Dilemmas in conceptualizing gender identity variants as psychiatric conditions. *Archives of Sexual Behavior*, 39(2), 461–476. doi:10.1007/s10508-009-9532-4
- Meyer-Bahlburg, H. F. L. (2011). Gender monitoring and gender reassignment of children and adolescents with a somatic disorder of sex development. *Child & Adolescent Psychiatric Clinics of North America*. 20(4), 639–649. doi: 10.1016/j.ch.2011.07.002.
- Meyer-Bahlburg, H. F. L., & Blizzard, R. M. (2004). Conference proceedings: Research on intersex: Summary of a planning workshop. *The Endocrinologist*, 14(2), 59–69. doi:10.1097/01.ten.0000123701.61007.4e
- Meyer-Bahlburg, H. F. L., Dolezal, C., Baker, S. W., Carlson, A. D., Obeid, J. S., & New, M. I. (2004). Prenatal androgenization affects gender-related behavior but not gender identity in 5–12-year-old girls with congenital adrenal hyperplasia. *Archives of Sexual Behavior*, 33(2), 97–104. doi:10.1023/B:ASEB.0000014324.25718.51

- Meyer-Bahlburg, H. F. L., Dolezal, C., Baker, S. W., Ehrhardt, A. A., & New, M. I. (2006). Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. *Archives of Sexual Behavior*, 35(6), 667–684. doi:10.1007/s10508-006-9068-9
- Meyer-Bahlburg, H. F. L., Migeon, C. J., Berkovitz, G. D., Gearhart, J. P., Dolezal, C., & Wisniewski, A. B. (2004). Attitudes of adult 46,XY intersex persons to clinical management policies. *The Journal of Urology*, 171(4), 1615–1619. doi:10.1097/01.ju.0000117761.94734.b7
- Money, J., & Ehrhardt, A. A. (1972). *Man and woman, boy and girl*. Baltimore, MD: Johns Hopkins University Press.
- Money, J., & Russo, A. J. (1979). Homosexual outcome of discordant gender identity/role in childhood: Longitudinal follow-up. *Journal of Pediatric Psychology*, 4(1), 29–41. doi:10.1093/jpepsy/4.1.29
- Monstrey, S., Hoebeke, P., Selvaggi, G., Ceulemans, P., Van Landuyt, K., Blondeel, P., . . . De Cuypere, G. (2009). Penile reconstruction: Is the radial forearm flap really the standard technique? *Plastic and Reconstructive Surgery*, 124(2), 510–518.
- Monstrey, S., Selvaggi, G., Ceulemans, P., Van Landuyt, K., Bowman, C., Blondeel, P., . . . De Cuypere, G. (2008). Chest-wall contouring surgery in female-to-male transsexuals: A new algorithm. *Plastic and Reconstructive Surgery*, 121(3), 849–859. doi:10.1097/01.prs.0000299921.15447.b2
- Moore, E., Wisniewski, A., & Dobs, A. (2003). Endocrine treatment of transsexual people: A review of treatment regimens, outcomes, and adverse effects. *Journal of Clinical Endocrinology & Metabolism*, 88(8), 3467–3473. doi:10.1210/jc.2002-021967
- More, S. D. (1998). The pregnant man – an oxymoron? *Journal of Gender Studies*, 7(3), 319–328. doi:10.1080/09589236.1998.9960725
- Mount, K. H., & Salmon, S. J. (1988). Changing the vocal characteristics of a postoperative transsexual patient: A longitudinal study. *Journal of Communication Disorders*, 21(3), 229–238. doi:10.1016/0021-9924(88)90031-7
- Mueller, A., Kiesewetter, F., Binder, H., Beckmann, M. W., & Dittrich, R. (2007). Long-term administration of testosterone undecanoate every 3 months for testosterone supplementation in female-to-male transsexuals. *Journal of Clinical Endocrinology & Metabolism*, 92(9), 3470–3475. doi:10.1210/jc.2007-0746
- Murad, M. H., Elamin, M. B., Garcia, M. Z., Mullan, R. J., Murad, A., Erwin, P. J., & Montori, V. M. (2010). Hormonal therapy and sex reassignment: A systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clinical Endocrinology*, 72(2), 214–231. doi:10.1111/j.1365-2265.2009.03625.x
- Nanda, S. (1998). *Neither man nor woman: The hijras of India*. Belmont, CA: Wadsworth.

- Nestle, J., Wilchins, R. A., & Howell, C. (2002). *Genderqueer: Voices from beyond the sexual binary*. Los Angeles, CA: Alyson Publications.
- Neumann, K., & Welzel, C. (2004). The importance of voice in male-to-female transsexualism. *Journal of Voice*, 18(1), 153–167.
- Newfield, E., Hart, S., Dibble, S., & Kohler, L. (2006). Female-to-male transgender quality of life. *Quality of Life Research*, 15(9), 1447–1457. doi:10.1007/s11136-006-0002-3
- Nieschlag, E., Behre, H. M., Bouchard, P., Corrales, J. J., Jones, T. H., Stalla, G. K., . . . Wu, F. C. W. (2004). Testosterone replacement therapy: Current trends and future directions. *Human Reproduction Update*, 10(5), 409–419. doi:10.1093/humupd/dmh035
- North American Menopause Society. (2010). Estrogen and progestogen use in postmenopausal women: 2010 position statement. *Menopause*, 17(2), 242–255. doi:10.1097/gme.0b013e3181d0f6b9
- Nuttbrock, L., Hwahng, S., Bockting, W., Rosenblum, A., Mason, M., Macri, M., & Becker, J. (2010). Psychiatric impact of gender-related abuse across the life course of male-to-female transgender persons. *Journal of Sex Research*, 47(1), 12–23. doi:10.1080/00224490903062258
- Oates, J. M., & Dacakis, G. (1983). Speech pathology considerations in the management of transsexualism—a review. *International Journal of Language & Communication Disorders*, 18(3), 139–151. doi:10.3109/13682828309012237
- Olyslager, F., & Conway, L. (2007). *On the calculation of the prevalence of transsexualism*. Paper presented at the World Professional Association for Transgender Health 20th International Symposium, Chicago, Illinois. Retrieved from http://www.changelingaspects.com/PDF/2007-09-06-Prevalence_of_Transsexualism.pdf
- Oriel, K. A. (2000). Clinical update: Medical care of transsexual patients. *Journal of the Gay and Lesbian Medical Association*, 4(4), 185–194. doi:1090-7173/00/1200-0185\$18.00/1
- Pauly, I. B. (1965). Male psychosexual inversion: Transsexualism: A review of 100 cases. *Archives of General Psychiatry*, 13(2), 172–181.
- Pauly, I. B. (1981). Outcome of sex reassignment surgery for transsexuals. *Australian and New Zealand Journal of Psychiatry*, 15(1), 45–51. doi:10.3109/00048678109159409
- Payer, A. F., Meyer, W. J. III, & Walker, P. A. (1979). The ultrastructural response of human leydig cells to exogenous estrogens. *Andrologia*, 11(6), 423–436. doi:10.1111/j.1439-0272.1979.tb02232.x

- Peletz, M. G. (2006). Transgenderism and gender pluralism in southeast Asia since early modern times. *Current Anthropology*, 47(2), 309–340. doi:10.1086/498947
- Pfäfflin, F. (1993). Regrets after sex reassignment surgery. *Journal of Psychology & Human Sexuality*, 5(4), 69–85.
- Pfäfflin, F., & Junge, A. (1998). Sex reassignment. Thirty years of international follow-up studies after sex reassignment surgery: A comprehensive review, 1961–1991. *International Journal of Transgenderism*. Retrieved from <http://web.archive.org/web/20070503090247/http://www.symposion.com/ijt/pfaefflin/1000.htm>
- Physicians' desk reference*. (61st ed.). (2007). Montvale, NJ: PDR.
- Physicians' desk reference*. (65th ed.). (2010). Montvale, NJ: PDR.
- Pleak, R. R. (1999). Ethical issues in diagnosing and treating gender-dysphoric children and adolescents. In M. Rottnek (Ed.), *Sissies and tomboys: Gender nonconformity and homosexual childhood* (pp. 34–51). New York: New York University Press.
- Pope, K. S., & Vasquez, M. J. (2011). *Ethics in psychotherapy and counseling: A practical guide* (4th ed.). Hoboken, NJ: John Wiley.
- Prior, J. C., Vigna, Y. M., & Watson, D. (1989). Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. *Archives of Sexual Behavior*, 18(1), 49–57. doi:10.1007/BF01579291
- Prior, J. C., Vigna, Y. M., Watson, D., Diwold, P., & Robinow, O. (1986). Spironolactone in the presurgical therapy of male to female transsexuals: Philosophy and experience of the Vancouver Gender Dysphoria Clinic. *Journal of Sex Information & Education Council of Canada*, 1, 1–7.
- Rachlin, K. (1999). Factors which influence individual's decisions when considering female-to-male genital reconstructive surgery. *International Journal of Transgenderism*, 3(3). Retrieved from <http://www.WPATH.org>
- Rachlin, K. (2002). Transgendered individuals' experiences of psychotherapy. *International Journal of Transgenderism*, 6(1). Retrieved from http://www.wpath.org/journal/www.iiav.nl/ezines/web/IJT/97-03/numbers/symposion/ijtvo06no01_03.htm.
- Rachlin, K., Green, J., & Lombardi, E. (2008). Utilization of health care among female-to-male transgender individuals in the United States. *Journal of Homosexuality*, 54(3), 243–258. doi:10.1080/00918360801982124

- Rachlin, K., Hansbury, G., & Pardo, S. T. (2010). Hysterectomy and oophorectomy experiences of female-to-male transgender individuals. *International Journal of Transgenderism*, 12(3), 155–166. doi:10.1080/15532739.2010.514220
- Reed, B., Rhodes, S., Schofield, P. & Wylie, K. (2009). *Gender variance in the UK: Prevalence, incidence, growth and geographic distribution*. Retrieved June 8, 2011, from <http://www.gires.org.uk/assets/Medpro-Assets/GenderVarianceUK-report.pdf>
- Rehman, J., Lazer, S., Benet, A. E., Schaefer, L. C., & Melman, A. (1999). The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Archives of Sexual Behavior*, 28(1), 71–89. doi:10.1023/A:1018745706354
- Robinow, O. (2009). Paraphilia and transgenderism: A connection with Asperger's disorder? *Sexual and Relationship Therapy*, 24(2), 143–151. doi:10.1080/14681990902951358
- Rosenberg, M. (2002). Children with gender identity issues and their parents in individual and group treatment. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41(5), 619–621. doi:10.1097/00004583-200205000-00020
- Rossouw, J. E., Anderson, G. L., Prentice, R. L., LaCroix, A. Z., Kooperberg, C., Stefanick, M. L., . . . Johnson, K. C. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. *JAMA: The Journal of the American Medical Association*, 288(3), 321–333.
- Royal College of Speech Therapists, United Kingdom. <http://www.rcslt.org/>
- Ruble, D. N., Martin, C. L., & Berenbaum, S. A. (2006). Gender development. In N. Eisenberg, W. Damon & R. M. Lerner (Eds.), *Handbook of child psychology* (6th ed., pp. 858–932). Hoboken, NJ: John Wiley.
- Sausa, L. A. (2005). Translating research into practice: Trans youth recommendations for improving school systems. *Journal of Gay & Lesbian Issues in Education*, 3(1), 15–28. doi:10.1300/J367v03n01_04
- Simpson, J. L., de la Cruz, F., Swerdloff, R. S., Samango-Sprouse, C., Skakkebaek, N. E., Graham, J. M. J., . . . Willard, H. F. (2003). Klinefelter syndrome: Expanding the phenotype and identifying new research directions. *Genetics in Medicine*, 5(6), 460–468. doi:10.1097/01.GIM.0000095626.54201.DO

- Smith, Y. L. S., Van Goozen, S. H. M., Kuiper, A. J., & Cohen-Kettenis, P. T. (2005). Sex reassignment: Outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychological Medicine*, 35(1), 89–99. doi:10.1017/S0033291704002776
- Sood, R., Shuster, L., Smith, R., Vincent, A., & Jatoi, A. (2011). Counseling postmenopausal women about bioidentical hormones: Ten discussion points for practicing physicians. *Journal of the American Board of Family Practice*, 24(2), 202–210. doi:10.3122/jabfm.2011.02.100194
- Speech Pathology Australia. <http://www.speechpathologyaustralia.org.au/>
- Speiser, P. W., Azziz, R., Baskin, L. S., Ghizzoni, L., Hensle, T. W., Merke, D. P., . . . Oberfield, S. E. (2010). Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An endocrine society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, 95(9), 4133–4160. doi:10.1210/jc.2009–2631
- Steensma, T. D., Biemond, R., de Boer, F., & Cohen-Kettenis, P. T. (2011). Desisting and persisting gender dysphoria after childhood: A qualitative follow-up study. *Clinical Child Psychology and Psychiatry*. Advance online publication. doi:10.1177/1359104510378303
- Steensma, T. D., & Cohen-Kettenis, P. T. (2011). Gender transitioning before puberty? *Archives of Sexual Behavior*, 40(4), 649–650. doi:10.1007/s10508–011–9752–2
- Stikkelbroeck, N. M. M. L., Beerendonk, C., Willemssen, W. N. P., Schreuders-Bais, C. A., Feitz, W. F. J., Rieu, P. N. M. A., . . . Otten, B. J. (2003). The long term outcome of feminizing genital surgery for congenital adrenal hyperplasia: Anatomical, functional and cosmetic outcomes, psychosexual development, and satisfaction in adult female patients. *Journal of Pediatric and Adolescent Gynecology*, 16(5), 289–296. doi:10.1016/S1083–3188(03)00155–4
- Stoller, R. J. (1964). A contribution to the study of gender identity. *International Journal of Psychoanalysis*, 45, 220–226.
- Stone, S. (1991). The empire strikes back: A posttranssexual manifesto. In J. Epstein, & K. Straub (Eds.), *Body guards: The cultural politics of gender ambiguity* (pp. 280–304). London: Routledge.
- Tangpricha, V., Ducharme, S. H., Barber, T. W., & Chipkin, S. R. (2003). Endocrinologic treatment of gender identity disorders. *Endocrine Practice*, 9(1), 12–21.
- Tangpricha, V., Turner, A., Malabanan, A., & Holick, M. (2001). Effects of testosterone therapy on bone mineral density in the FtM patient. *International Journal of Transgenderism*, 5(4).
- Taywaditep, K. J., Coleman, E., & Dumronggittigule, P. (1997). Thailand (Muang Thai). In R. Francoeur (Ed.), *International encyclopedia of sexuality*. New York, NY: Continuum.

- Thole, Z., Manso, G., Salgueiro, E., Revuelta, P., & Hidalgo, A. (2004). Hepatotoxicity induced by antiandrogens: A review of the literature. *Urologia Internationalis*, 73(4), 289–295. doi:10.1159/000081585
- Tom Waddell Health Center. (2006). *Protocols for hormonal reassignment of gender*. Retrieved from <http://www.sfdph.org/dph/comupg/oservices/medSvs/hlthCtrs/TransGendprotocols122006.pdf>
- Tsoi, W. F. (1988). The prevalence of transsexualism in Singapore. *Acta Psychiatrica Scandinavica*, 78(4), 501–504. doi:10.1111/j.1600-0447.1988.tb06373.x
- Van den Broecke, R., Van der Elst, J., Liu, J., Hovatta, O., & Dhont, M. (2001). The female-to-male transsexual patient: A source of human ovarian cortical tissue for experimental use. *Human Reproduction*, 16(1), 145–147. doi:10.1093/humrep/16.1.145
- Vanderburgh, R. (2009). Appropriate therapeutic care for families with pre-pubescent transgender/gender-dissonant children. *Child and Adolescent Social Work Journal*, 26(2), 135–154. doi:10.1007/s10560-008-0158-5
- van Kesteren, P. J. M., Asscheman, H., Megens, J. A. J., & Gooren, L. J. G. (1997). Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clinical Endocrinology*, 47(3), 337–343. doi:10.1046/j.1365-2265.1997.2601068.x
- van Kesteren, P. J. M., Gooren, L. J., & Megens, J. A. (1996). An epidemiological and demographic study of transsexuals in the Netherlands. *Archives of Sexual Behavior*, 25(6), 589–600. doi:10.1007/BF02437841
- van Trotsenburg, M. A. A. (2009). Gynecological aspects of transgender healthcare. *International Journal of Transgenderism*, 11(4), 238–246. doi:10.1080/15532730903439484
- Vilain, E. (2000). Genetics of sexual development. *Annual Review of Sex Research*, 11, 1–25.
- Wålinder, J. (1968). Transsexualism: Definition, prevalence and sex distribution. *Acta Psychiatrica Scandinavica*, 43(S203), 255–257.
- Wålinder, J. (1971). Incidence and sex ratio of transsexualism in Sweden. *The British Journal of Psychiatry*, 119(549), 195–196.
- Wallien, M. S. C., & Cohen-Kettenis, P. T. (2008). Psychosexual outcome of gender-dysphoric children. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47(12), 1413–1423. doi:10.1097/CHI.0b013e31818956b9
- Wallien, M. S. C., Swaab, H., & Cohen-Kettenis, P. T. (2007). Psychiatric comorbidity among children with gender identity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46(10), 1307–1314. doi:10.1097/chi.0b013e3181373848

- Warren, B. E. (1993). Transsexuality, identity and empowerment. A view from the frontlines. *SIECUS Report, February/March*, 14–16.
- Weitze, C., & Osburg, S. (1996). Transsexualism in Germany: Empirical data on epidemiology and application of the German Transsexuals' Act during its first ten years. *Archives of Sexual Behavior*, 25(4), 409–425.
- Wilson, J. D. (1999). The role of androgens in male gender role behavior. *Endocrine Reviews*, 20(5), 726–737. doi:10.1210/er.20.5.726
- Winter, S. (2009). Cultural considerations for The World Professional Association for Transgender Health's *standards of care*: The Asian perspective. *International Journal of Transgenderism*, 11(1), 19–41. doi:10.1080/15532730902799938
- Winter, S., Chalungsooth, P., Teh, Y. K., Rojanalert, N., Maneerat, K., Wong, Y. W., . . . Macapagal, R. A. (2009). Transpeople, transprejudice and pathologization: A seven-country factor analytic study. *International Journal of Sexual Health*, 21(2), 96–118. doi:10.1080/19317610902922537
- Wisniewski, A. B., Migeon, C. J., Malouf, M. A., & Gearhart, J. P. (2004). Psychosexual outcome in women affected by congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *The Journal of Urology*, 171(6, Part 1), 2497–2501. doi:10.1097/01.ju.0000125269.91938.f7
- World Health Organization. (2007). *International classification of diseases and related health problems-10th revision*. Geneva, Switzerland: World Health Organization.
- World Health Organization. (2008). *The world health report 2008: Primary health care—now more than ever*. Geneva, Switzerland: World Health Organization.
- World Professional Association for Transgender Health, Inc. (2008). *WPATH clarification on medical necessity of treatment, sex reassignment, and insurance coverage in the U.S.A*. Retrieved from <http://www.wpath.org/documents/Med%20Nec%20on%202008%20Letterhead.pdf>
- WPATH Board of Directors. (2010). *De-psychopathologisation statement released May 26, 2010*. Retrieved from http://wpath.org/announcements_detail.cfm?pk_announcement=17
- Xavier, J. M. (2000). *The Washington, D.C. transgender needs assessment survey: Final report for phase two*. Washington, DC: Administration for HIV/AIDS of District of Columbia Government.
- Zhang, G., Gu, Y., Wang, X., Cui, Y., & Bremner, W. J. (1999). A clinical trial of injectable testosterone undecanoate as a potential male contraceptive in normal Chinese men. *Journal of Clinical Endocrinology & Metabolism*, 84(10), 3642–3647. doi:10.1210/jc.84.10.3642

- Zitzmann, M., Saad, F., & Nieschlag, E. (2006, April). *Long term experience of more than 8 years with a novel formulation of testosterone undecanoate (nebido) in substitution therapy of hypogonadal men*. Paper presented at European Congress of Endocrinology, Glasgow, UK.
- Zucker, K. J. (1999). Intersexuality and gender identity differentiation. *Annual Review of Sex Research, 10*(1), 1–69.
- Zucker, K. J. (2004). Gender identity development and issues. *Child and Adolescent Psychiatric Clinics of North America, 13*(3), 551–568. doi:10.1016/j.chc.2004.02.006
- Zucker, K. J. (2006). “I’m half-boy, half-girl”: Play psychotherapy and parent counseling for gender identity disorder. In R. L. Spitzer, M. B. First, J. B. W. Williams & M. Gibbons (Eds.), *DSM-IV-TR casebook, volume 2* (pp. 321–334). Arlington, VA: American Psychiatric Publishing, Inc.
- Zucker, K. J. (2010). The DSM diagnostic criteria for gender identity disorder in children. *Archives of Sexual Behavior, 39*(2), 477–498. doi:10.1007/s10508-009-9540-4
- Zucker, K. J., & Bradley, S. J. (1995). *Gender identity disorder and psychosexual problems in children and adolescents*. New York, NY: Guilford Press.
- Zucker, K. J., Bradley, S. J., Owen-Anderson, A., Kibblewhite, S. J., & Cantor, J. M. (2008). Is gender identity disorder in adolescents coming out of the closet? *Journal of Sex & Marital Therapy, 34*(4), 287–290. doi:10.1080/00926230802096192
- Zucker, K. J., Bradley, S. J., Owen-Anderson, A., Kibblewhite, S. J., Wood, H., Singh, D., & Choi, K. (in press). Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. *Journal of Sex & Marital Therapy, 38*(2), 151–189.
- Zucker, K. J., & Lawrence, A. A. (2009). Epidemiology of gender identity disorder: Recommendations for the *standards of care* of The World Professional Association for Transgender Health. *International Journal of Transgenderism, 11*(1), 8–18. doi:10.1080/15532730902799946
- Zucker, K. J., Owen, A., Bradley, S. J., & Ameeriar, L. (2002). Gender-dysphoric children and adolescents: A comparative analysis of demographic characteristics and behavioral problems. *Clinical Child Psychology and Psychiatry, 7*(3), 398–411.
- Zuger, B. (1984). Early effeminate behavior in boys: Outcome and significance for homosexuality. *Journal of Nervous and Mental Disease, 172*(2), 90–97.

APPENDIX A

GLOSSARY

Terminology in the area of health care for transsexual, transgender, and gender-nonconforming people is rapidly evolving; new terms are being introduced, and the definitions of existing terms are changing. Thus, there is often misunderstanding, debate, or disagreement about language in this field. Terms that may be unfamiliar or that have specific meanings in the SOC are defined below for the purpose of this document only. Others may adopt these definitions, but WPATH acknowledges that these terms may be defined differently in different cultures, communities, and contexts.

WPATH also acknowledges that many terms used in relation to this population are not ideal. For example, the terms *transsexual* and *transvestite*—and, some would argue, the more recent term *transgender*—have been applied to people in an objectifying fashion. Yet such terms have been more or less adopted by many people who are making their best effort to make themselves understood. By continuing to use these terms, WPATH intends only to ensure that concepts and processes are comprehensible, in order to facilitate the delivery of quality health care to transsexual, transgender, and gender-nonconforming people. WPATH remains open to new terminology that will further illuminate the experience of members of this diverse population and lead to improvements in health care access and delivery.

Bioidentical hormones: Hormones that are *structurally* identical to those found in the human body (ACOG Committee of Gynecologic Practice, 2005). The hormones used in bioidentical hormone therapy (BHT) are generally derived from plant sources and are structurally similar to endogenous human hormones, but they need to be commercially processed to become bioidentical.

Bioidentical compounded hormone therapy (BCHT): Use of hormones that are prepared, mixed, assembled, packaged, or labeled as a drug by a pharmacist and custom-made for a patient according to a physician's specifications. Government drug agency approval is not possible for each compounded product made for an individual consumer.

Cross-dressing (transvestism): Wearing clothing and adopting a gender role presentation that, in a given culture, is more typical of the other sex.

Disorders of sex development (DSD): Congenital conditions in which the development of chromosomal, gonadal, or anatomic sex is atypical. Some people strongly object to the “disorder” label and instead view these conditions as a matter of diversity (Diamond, 2009), preferring the terms *intersex* and *intersexuality*.

Female-to-Male (FtM): Adjective to describe individuals assigned female at birth who are changing or who have changed their body and/or gender role from birth-assigned female to a more masculine body or role.

Gender dysphoria: Distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).

Gender identity: A person's intrinsic sense of being male (a boy or a man), female (a girl or woman), or an alternative gender (e.g., boygirl, girlboy, transgender, genderqueer, eunuch) (Bockting, 1999; Stoller, 1964).

Gender identity disorder: Formal diagnosis set forth by the *Diagnostic Statistical Manual of Mental Disorders, 4th Edition, Text Rev (DSM IV-TR)* (American Psychiatric Association, 2000). Gender identity disorder is characterized by a strong and persistent cross-gender identification and a persistent discomfort with one's sex or sense of inappropriateness in the gender role of that sex, causing clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Gender-nonconforming: Adjective to describe individuals whose gender identity, role, or expression differs from what is normative for their assigned sex in a given culture and historical period.

Gender role or expression: Characteristics in personality, appearance, and behavior that in a given culture and historical period are designated as masculine or feminine (that is, more typical of the male or female social role) (Ruble, Martin, & Berenbaum, 2006). While most individuals present socially in clearly masculine or feminine gender roles, some people present in an alternative gender role such as genderqueer or specifically transgender. All people tend to incorporate both masculine and feminine characteristics in their gender expression in varying ways and to varying degrees (Bockting, 2008).

Genderqueer: Identity label that may be used by individuals whose gender identity and/or role does not conform to a binary understanding of gender as limited to the categories of man or woman, male or female (Bockting, 2008).

Internalized transphobia: Discomfort with one's own transgender feelings or identity as a result of internalizing society's normative gender expectations.

Male-to-Female (MtF): Adjective to describe individuals assigned male at birth who are changing or who have changed their body and/or gender role from birth-assigned male to a more feminine body or role.

Natural hormones: Hormones that are derived from natural *sources* such as plants or animals. Natural hormones may or may not be bioidentical.

Sex: Sex is assigned at birth as male or female, usually based on the appearance of the external genitalia. When the external genitalia are ambiguous, other components of sex (internal genitalia, chromosomal and hormonal sex) are considered in order to assign sex (Grumbach, Hughes, & Conte, 2003; MacLaughlin & Donahoe, 2004; Money & Ehrhardt, 1972; Vilain, 2000). For most people, gender identity and expression are consistent with their sex assigned at birth; for transsexual, transgender, and gender-nonconforming individuals, gender identity or expression differ from their sex assigned at birth.

Sex reassignment surgery (gender affirmation surgery): Surgery to change primary and/or secondary sex characteristics to affirm a person's gender identity. Sex reassignment surgery can be an important part of medically necessary treatment to alleviate gender dysphoria.

Transgender: Adjective to describe a diverse group of individuals who cross or transcend culturally defined categories of gender. The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth (Bockting, 1999).

Transition: Period of time when individuals change from the gender role associated with their sex assigned at birth to a different gender role. For many people, this involves learning how to live socially in another gender role; for others this means finding a gender role and expression that are most comfortable for them. Transition may or may not include feminization or masculinization of the body through hormones or other medical procedures. The nature and duration of transition are variable and individualized.

Transsexual: Adjective (often applied by the medical profession) to describe individuals who seek to change or who have changed their primary and/or secondary sex characteristics through feminizing or masculinizing medical interventions (hormones and/or surgery), typically accompanied by a permanent change in gender role.

APPENDIX B

OVERVIEW OF MEDICAL RISKS OF HORMONE THERAPY

The risks outlined below are based on two comprehensive, evidence-based literature reviews of masculinizing/feminizing hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009), along with a large cohort study (Asscheman et al., 2011). These reviews can serve as detailed references for providers, along with other widely recognized, published clinical materials (e.g., Dahl et al., 2006; Ettner et al., 2007).

Risks of Feminizing Hormone Therapy (MtF)

Likely Increased Risk:

Venous thromboembolic disease

- Estrogen use increases the risk of venous thromboembolic events (VTE), particularly in patients who are over age 40, smokers, highly sedentary, obese, and who have underlying thrombophilic disorders.
- This risk is increased with the additional use of third generation progestins.
- This risk is decreased with use of the transdermal (versus oral) route of estradiol administration, which is recommended for patients at higher risk of VTE.

Cardiovascular, cerebrovascular disease

- Estrogen use increases the risk of cardiovascular events in patients over age 50 with underlying cardiovascular risk factors. Additional progestin use may increase this risk.

Lipids

- Oral estrogen use may markedly increase triglycerides in patients, increasing the risk of pancreatitis and cardiovascular events.
- Different routes of administration will have different metabolic effects on levels of HDL cholesterol, LDL cholesterol and lipoprotein(a).
- In general, clinical evidence suggests that MtF patients with pre-existing lipid disorders may benefit from the use of transdermal rather than oral estrogen.

Liver/gallbladder

- Estrogen and cyproterone acetate use may be associated with transient liver enzyme elevations and, rarely, clinical hepatotoxicity.
- Estrogen use increases the risk of cholelithiasis (gall stones) and subsequent cholecystectomy.

Possible Increased Risk:Type 2 diabetes mellitus

- Feminizing hormone therapy, particularly estrogen, may increase the risk of type 2 diabetes, particularly among patients with a family history of diabetes or other risk factors for this disease.

Hypertension

- Estrogen use may increase blood pressure, but the effect on incidence of overt hypertension is unknown.
- Spironolactone reduces blood pressure and is recommended for at-risk or hypertensive patients desiring feminization.

Prolactinoma

- Estrogen use increases the risk of hyperprolactinemia among MtF patients in the first year of treatment, but this risk is unlikely thereafter.
- High-dose estrogen use may promote the clinical appearance of preexisting but clinically unapparent prolactinoma.

Inconclusive or No Increased Risk:

Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Breast cancer

- MtF persons who have taken feminizing hormones do experience breast cancer, but it is unknown how their degree of risk compares to that of persons born with female genitalia.
- Longer duration of feminizing hormone exposure (i.e., number of years taking estrogen preparations), family history of breast cancer, obesity (BMI >35), and the use of progestins likely influence the level of risk.

Other Side Effects of Feminizing Therapy:

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with feminizing hormone therapy.

Fertility and sexual function

- Feminizing hormone therapy may impair fertility.
- Feminizing hormone therapy may decrease libido.
- Feminizing hormone therapy reduces nocturnal erections, with variable impact on sexually stimulated erections.

Risks of Anti-Androgen Medications:

Feminizing hormone regimens often include a variety of agents that affect testosterone production or action. These include GnRH agonists, progestins (including cyproterone acetate), spironolactone, and 5-alpha reductase inhibitors. An extensive discussion of the specific risks of these agents is beyond the scope of the SOC. However, both spironolactone and cyproterone acetate are widely used and deserve some comment.

Cyproterone acetate is a progestational compound with anti-androgenic properties (Gooren, 2005; Levy et al., 2003). Although widely used in Europe, it is not approved for use in the United States because of concerns about hepatotoxicity (Thole, Manso, Salgueiro, Revuelta, & Hidalgo, 2004). Spironolactone is commonly used as an anti-androgen in feminizing hormone therapy, particularly in regions where cyproterone is not approved for use (Dahl et al., 2006; Moore et al., 2003; Tangpricha et al., 2003). Spironolactone has a long history of use in treating hypertension and congestive heart failure. Its common side effects include hyperkalemia, dizziness, and gastrointestinal symptoms (*Physicians' Desk Reference*, 2007).

Risks of Masculinizing Hormone Therapy (FtM)

Likely Increased Risk:

Polycythemia

- Masculinizing hormone therapy involving testosterone or other androgenic steroids increases the risk of polycythemia (hematocrit > 50%), particularly in patients with other risk factors.
- Transdermal administration and adaptation of dosage may reduce this risk.

Weight gain/visceral fat

- Masculinizing hormone therapy can result in modest weight gain, with an increase in visceral fat.

Possible Increased Risk:

Lipids

- Testosterone therapy decreases HDL, but variably affects LDL and triglycerides.
- Supraphysiologic (beyond normal male range) serum levels of testosterone, often found with extended intramuscular dosing, may worsen lipid profiles, whereas transdermal administration appears to be more lipid neutral.
- Patients with underlying polycystic ovarian syndrome or dyslipidemia may be at increased risk of worsening dyslipidemia with testosterone therapy.

Liver

- Transient elevations in liver enzymes may occur with testosterone therapy.
- Hepatic dysfunction and malignancies have been noted with oral methyltestosterone. However, methyltestosterone is no longer available in most countries and should no longer be used.

Psychiatric

Masculinizing therapy involving testosterone or other androgenic steroids may increase the risk of hypomanic, manic, or psychotic symptoms in patients with underlying psychiatric disorders that include such symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

Inconclusive or No Increased Risk:

Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Osteoporosis

- Testosterone therapy maintains or increases bone mineral density among FtM patients prior to oophorectomy, at least in the first three years of treatment.
- There is an increased risk of bone density loss after oophorectomy, particularly if testosterone therapy is interrupted or insufficient. This includes patients utilizing solely oral testosterone.

Cardiovascular

- Masculinizing hormone therapy at normal physiologic doses does not appear to increase the risk of cardiovascular events among healthy patients.
- Masculinizing hormone therapy may increase the risk of cardiovascular disease in patients with underlying risks factors.

Hypertension

- Masculinizing hormone therapy at normal physiologic doses may increase blood pressure but does not appear to increase the risk of hypertension.
- Patients with risk factors for hypertension, such as weight gain, family history, or polycystic ovarian syndrome, may be at increased risk.

Type 2 diabetes mellitus

- Testosterone therapy does not appear to increase the risk of type 2 diabetes among FtM patients overall, unless other risk factors are present.
- Testosterone therapy may further increase the risk of type 2 diabetes in patients with other risk factors, such as significant weight gain, family history, and polycystic ovarian syndrome. There are no data that suggest or show an increase in risk in those with risk factors for dyslipidemia.

Breast cancer

- Testosterone therapy in FtM patients does not increase the risk of breast cancer.

Cervical cancer

- Testosterone therapy in FtM patients does not increase the risk of cervical cancer, although it may increase the risk of minimally abnormal Pap smears due to atrophic changes.

Ovarian cancer

- Analogous to persons born with female genitalia with elevated androgen levels, testosterone therapy in FtM patients may increase the risk of ovarian cancer, although evidence is limited.

Endometrial (uterine) cancer

- Testosterone therapy in FtM patients may increase the risk of endometrial cancer, although evidence is limited.

Other Side Effects of Masculinizing Therapy:

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with masculinization.

Fertility and sexual function

- Testosterone therapy in FtM patients reduces fertility, although the degree and reversibility are unknown.

- Testosterone therapy can induce permanent anatomic changes in the developing embryo or fetus.
- Testosterone therapy induces clitoral enlargement and increases libido.

Acne, androgenic alopecia

Acne and varying degrees of male pattern hair loss (androgenic alopecia) are common side effects of masculinizing hormone therapy.

APPENDIX C

SUMMARY OF CRITERIA FOR HORMONE THERAPY AND SURGERIES

As for all previous versions of the SOC, the criteria put forth in the SOC for hormone therapy and surgical treatments for gender dysphoria are clinical guidelines; individual health professionals and programs may modify them. Clinical departures from the SOC may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, explained to the patient, and documented through informed consent for quality patient care and legal protection. This documentation is also valuable to accumulate new data, which can be retrospectively examined to allow for health care—and the SOC—to evolve.

Criteria for Feminizing/Masculinizing Hormone Therapy (One Referral or Chart Documentation of Psychosocial Assessment)

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental concerns are present, they must be reasonably well controlled.

Criteria for Breast/Chest Surgery (One Referral)

Mastectomy and Creation of a Male Chest in FtM Patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a prerequisite.

Breast Augmentation (Implants/Lipofilling) in MtF Patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Criteria for Genital Surgery (Two Referrals)

Hysterectomy and Salpingo-Oophorectomy in FtM Patients and Orchiectomy in MtF Patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;

3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual).

The aim of hormone therapy prior to gonadectomy is primarily to introduce a period of reversible estrogen or testosterone suppression, before a patient undergoes irreversible surgical intervention.

These criteria do not apply to patients who are having these surgical procedures for medical indications other than gender dysphoria.

Metoidioplasty or Phalloplasty in FtM Patients and Vaginoplasty in MtF Patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to give consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless hormones are not clinically indicated for the individual);
6. 12 continuous months of living in a gender role that is congruent with their gender identity.

Although not an explicit criterion, it is recommended that these patients also have regular visits with a mental health or other medical professional.

The criterion noted above for some types of genital surgeries—that is, that patients engage in 12 continuous months of living in a gender role that is congruent with their gender identity—is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery.

APPENDIX D

EVIDENCE FOR CLINICAL OUTCOMES OF THERAPEUTIC APPROACHES

One of the real supports for any new therapy is an outcome analysis. Because of the controversial nature of sex reassignment surgery, this type of analysis has been very important. Almost all of the outcome studies in this area have been retrospective.

One of the first studies to examine the post-treatment psychosocial outcomes of transsexual patients was done in 1979 at Johns Hopkins University School of Medicine and Hospital (USA) (J. K. Meyer & Reter, 1979). This study focused on patients' occupational, educational, marital, and domiciliary stability. The results revealed several significant changes with treatment. These changes were not seen as positive; rather, they showed that many individuals who had entered the treatment program were no better off or were worse off in many measures after participation in the program. These findings resulted in closure of the treatment program at that hospital/medical school (Abramowitz, 1986).

Subsequently, a significant number of health professionals called for a standard for eligibility for sex reassignment surgery. This led to the formulation of the original *Standards of Care* of the Harry Benjamin International Gender Dysphoria Association (now WPATH) in 1979.

In 1981, Pauly published results from a large retrospective study of people who had undergone sex reassignment surgery. Participants in that study had much better outcomes: Among 83 FtM patients, 80.7% had a satisfactory outcome (i.e., patient self report of "improved social and emotional adjustment"), 6.0% unsatisfactory. Among 283 MtF patients, 71.4% had a satisfactory outcome, 8.1% unsatisfactory. This study included patients who were treated before the publication and use of the *Standards of Care*.

Since the *Standards of Care* have been in place, there has been a steady increase in patient satisfaction and decrease in dissatisfaction with the outcome of sex reassignment surgery. Studies conducted after 1996 focused on patients who were treated according to the *Standards of Care*. The findings of Rehman and colleagues (1999) and Krege and colleagues (2001) are typical of this body of work; none of the patients in these studies regretted having had surgery, and most reported being satisfied with the cosmetic and functional results of the surgery. Even patients who develop severe surgical complications seldom regret having undergone surgery. Quality of surgical results is one of the best predictors of the overall outcome of sex reassignment (Lawrence, 2003). The vast majority of follow-up studies have shown an undeniable beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective well being, cosmesis, and sexual function (De Cuypere et al., 2005; Garaffa, Christopher, & Ralph, 2010; Klein & Gorzalka, 2009), although the specific magnitude of benefit is uncertain from

the currently available evidence. One study (Emory, Cole, Avery, Meyer, & Meyer, 2003) even showed improvement in patient income.

One troubling report (Newfield et al., 2006) documented lower scores on quality of life (measured with the SF-36) for FtM patients than for the general population. A weakness of that study is that it recruited its 384 participants by a general email rather than a systematic approach, and the degree and type of treatment were not recorded. Study participants who were taking testosterone had typically been doing so for less than 5 years. Reported quality of life was higher for patients who had undergone breast/chest surgery than for those who had not ($p < .001$). (A similar analysis was not done for genital surgery.) In other work, Kuhn and colleagues (2009) used the King's Health Questionnaire to assess the quality of life of 55 transsexual patients at 15 years after surgery. Scores were compared to those of 20 healthy female control patients who had undergone abdominal/pelvic surgery in the past. Quality of life scores for transsexual patients were the same or better than those of control patients for some subscales (emotions, sleep, incontinence, symptom severity, and role limitation), but worse in other domains (general health, physical limitation, and personal limitation).

Two long-term observational studies, both retrospective, compared the mortality and psychiatric morbidity of transsexual adults to those of general population samples (Asscheman et al., 2011; Dhejne et al., 2011). An analysis of data from the Swedish National Board of Health and Welfare information registry found that individuals who had received sex reassignment surgery (191 MtF and 133 FtM) had significantly higher rates of mortality, suicide, suicidal behavior, and psychiatric morbidity than those for a nontranssexual control group matched on age, immigrant status, prior psychiatric morbidity, and birth sex (Dhejne et al., 2011). Similarly, a study in the Netherlands reported a higher total mortality rate, including incidence of suicide, in both pre- and post-surgery transsexual patients (966 MtF and 365 FtM) than in the general population of that country (Asscheman et al., 2011). Neither of these studies questioned the efficacy of sex reassignment; indeed, both lacked an adequate comparison group of transsexuals who either did not receive treatment or who received treatment other than genital surgery. Moreover, transsexual people in these studies were treated as far back as the 1970s. However, these findings do emphasize the need to have good long-term psychological and psychiatric care available for this population. More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria.

It is difficult to determine the effectiveness of hormones alone in the relief of gender dysphoria. Most studies evaluating the effectiveness of masculinizing/feminizing hormone therapy on gender dysphoria have been conducted with patients who have also undergone sex reassignment surgery. Favorable effects of therapies that included both hormones and surgery were reported in a comprehensive review of over 3000 patients in 79 studies (mostly observational) conducted between 1961 and 1991 (Eldh, Berg, & Gustafsson, 1997; Gijs & Brewaeys, 2007; Murad et al., 2010; Pfäfflin & Junge, 1998). Patients operated on after 1986 did better than those before 1986; this reflects significant improvement in surgical complications (Eldh et al., 1997). Most patients have reported improved psychosocial outcomes, ranging between 87% for MtF patients and 97% for FtM patients (Green & Fleming, 1990).

Similar improvements were found in a Swedish study in which “almost all patients were satisfied with sex reassignment at 5 years, and 86% were assessed by clinicians at follow-up as stable or improved in global functioning” (Johansson, Sundbom, Höjerback, & Bodlund, 2010). Weaknesses of these earlier studies are their retrospective design and use of different criteria to evaluate outcomes.

A prospective study conducted in the Netherlands evaluated 325 consecutive adult and adolescent subjects seeking sex reassignment (Smith, Van Goozen, Kuiper, & Cohen-Kettenis, 2005). Patients who underwent sex reassignment therapy (both hormonal and surgical intervention) showed improvements in their mean gender dysphoria scores, measured by the Utrecht Gender Dysphoria Scale. Scores for body dissatisfaction and psychological function also improved in most categories. Fewer than 2% of patients expressed regret after therapy. This is the largest prospective study to affirm the results from retrospective studies that a combination of hormone therapy and surgery improves gender dysphoria and other areas of psychosocial functioning. There is a need for further research on the effects of hormone therapy without surgery, and without the goal of maximum physical feminization or masculinization.

Overall, studies have been reporting a steady improvement in outcomes as the field becomes more advanced. Outcome research has mainly focused on the outcome of sex reassignment surgery. In current practice there is a range of identity, role, and physical adaptations that could use additional follow-up or outcome research (Institute of Medicine, 2011).

APPENDIX E

DEVELOPMENT PROCESS FOR THE STANDARDS OF CARE, VERSION 7

The process of developing *Standards of Care, Version 7* began when an initial SOC “work group” was established in 2006. Members were invited to examine specific sections of SOC, *Version 6*. For each section, they were asked to review the relevant literature, identify where research was lacking and needed, and recommend potential revisions to the SOC as warranted by new evidence. Invited papers were submitted by the following authors: Aaron Devor, Walter Bockting, George Brown, Michael Brownstein, Peggy Cohen-Kettenis, Griet DeCuypere, Petra DeSutter, Jamie Feldman, Lin Fraser, Arlene Istar Lev, Stephen Levine, Walter Meyer, Heino Meyer-Bahlburg, Stan Monstrey, Loren Schechter, Mick van Trotsenburg, Sam Winter, and Ken Zucker. Some of these authors chose to add co-authors to assist them in their task.

Initial drafts of these papers were due June 1, 2007. Most were completed by September 2007, with the rest completed by the end of 2007. These manuscripts were then submitted to the *International*

Journal of Transgenderism (IJT). Each underwent the regular *IJT* peer review process. The final papers were published in Volume 11 (1–4) in 2009, making them available for discussion and debate.

After these articles were published, an SOC Revision Committee was established by the WPATH Board of Directors in 2010. The Revision Committee was first charged with debating and discussing the *IJT* background papers through a Google website. A subgroup of the Revision Committee was appointed by the Board of Directors to serve as the Writing Group. This group was charged with preparing the first draft of SOC, *Version 7* and continuing to work on revisions for consideration by the broader Revision Committee. The Board also appointed an International Advisory Group of transsexual, transgender, and gender-nonconforming individuals to give input on the revision.

A technical writer was hired to (1) review all of the recommendations for revision—both the original recommendations as outlined in the *IJT* articles and additional recommendations that emanated from the online discussion—and (2) create a survey to solicit further input on these potential revisions. From the survey results, the Writing Group was able to discern where these experts stood in terms of areas of agreement and areas in need of more discussion and debate. The technical writer then (3) created a very rough first draft of SOC, *Version 7* for the Writing Group to consider and build on.

The Writing Group met on March 4 and 5, 2011 in a face-to-face expert consultation meeting. They reviewed all recommended changes and debated and came to consensus on various controversial areas. Decisions were made based on the best available science and expert consensus. These decisions were incorporated into the draft, and additional sections were written by the Writing Group with the assistance of the technical writer.

The draft that emerged from the consultation meeting was then circulated among the Writing Group and finalized with the help of the technical writer. Once this initial draft was finalized, it was circulated among the broader SOC Revision Committee and the International Advisory Group. Discussion was opened up on the Google website and a conference call was held to resolve issues. Feedback from these groups was considered by the Writing Group, who then made further revisions. Two additional drafts were created and posted on the Google website for consideration by the broader SOC Revision Committee and the International Advisory Group. Upon completion of these three iterations of review and revision, the final document was presented to the WPATH Board of Directors for approval. The Board of Directors approved this version on September 14, 2011.

Funding

The *Standards of Care* revision process was made possible through a generous grant from the Tawani Foundation and a gift from an anonymous donor. These funds supported the following:

1. Costs of a professional technical writer;
2. Process of soliciting international input on proposed changes from gender identity professionals and the transgender community;
3. Working meeting of the Writing Group;
4. Process of gathering additional feedback and arriving at final expert consensus from the professional and transgender communities, the *Standards of Care, Version 7*, Revision Committee, and WPATH Board of Directors;
5. Costs of printing and distributing *Standards of Care, Version 7*, and posting a free downloadable copy on the WPATH website;
6. Plenary session to launch the *Standards of Care, Version 7*, at the 2011 WPATH Biennial Symposium in Atlanta, Georgia, USA.

Members of the *Standards of Care* Revision Committee[†]

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† All members of the *Standards of Care, Version 7* Revision Committee donated their time to work on this revision.

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Proposed Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

In the absence of a NCD, initial coverage determinations under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements will be made by the local Medicare Administrative Contractors (MACs) on an individual claim basis.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform the answer to the question posed in this proposed decision memorandum. Based on the gaps identified in the clinical evidence, these studies should focus on which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be developed that would support coverage with evidence development (CED), which would only cover gender reassignment surgery for beneficiaries who choose to participate in a clinical study.

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Proposed Decision Memo

App. 588

From: Tamara Syrek Jensen, JD
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Analyst

Subject: Proposed Decision Memorandum on Gender Reassignment Surgery for Medicare Beneficiaries with Gender Dysphoria

Date: June 2, 2016

I. Proposed Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

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We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be conducted.

II. Background

Below is a list of acronyms used throughout this document.

AHRQ - Agency for Healthcare Research and Quality
 AIDS - Acquired Immune Deficiency Syndrome
 ANOVA - Analysis of Variance
 APA - American Psychiatric Association
 APGAR - Adaptability, Partnership Growth, Affection, and Resolve test
 BIQ - Body Image Questionnaire
 BSRI - Bem Sex Role Inventory
 CCEI - Crown Craps Experimental Index
 CHIS - California Health Interview Survey
 CI - Confidence Interval
 CMS - Centers for Medicare & Medicaid Services
 DAB - Departmental Appeals Board
 DSM - Diagnostic and Statistical Manual of Mental Disorders
 EMBASE - Excerpta Medica dataBASE
 FBeK - Fragebogen zur Beurteilung des eigenen Körpers
 FDA - Food and Drug Administration
 FPI-R - Freiburg Personality Inventory
 FSFI - Female Sexual Function Index
 GAF - Global Assessment of Functioning
 GID - Gender Identity Disorder
 GIS - Gender Identity Trait Scale
 GRS - Gender Reassignment Surgery
 GSI - Global Severity Indices
 HADS - Hospital Anxiety Depression Scale
 HHS - U.S. Department of Health and Human Services
 HIV - Human Immunodeficiency Virus
 IIP - Inventory of Interpersonal Problems
 IOM - Institute of Medicine
 KHQ - King's Health Questionnaire
 LGB - Lesbian, Gay, and Bisexual
 LGBT - Lesbian, Gay, Bisexual, and Transgender
 MAC - Medicare Administrative Contractor
 MMPI - Minnesota Multiphasic Personality Inventory
 NCA - National Coverage Analysis
 NCD - National Coverage Determination
 NICE - National Institute for Health Care Excellence
 NIH - National Institutes of Health
 NZHTA - New Zealand Health Technology Assessment
 PIT - Psychological Integration of Trans-sexuals
 QOL - Quality of Life
 S.D. - Standard Deviation
 SADS - Social Anxiety Depression Scale
 SCL-90R - Symptom Check List 90-Revised
 SDPE - Scale for Depersonalization Experiences
 SES - Self Esteem Scale
 SF - Short Form
 SMR - Standardized Mortality Ratio
 SOC - Standards of Care
 STAI-X1 - Spielberger State and Trait Anxiety Questionnaire
 STAI-X2 - Spielberger State and Trait Anxiety Questionnaire

A. Diagnostic Criteria

The criteria for gender dysphoria or spectrum of related conditions as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has changed over time (See Appendix A).

Gender dysphoria (previously known as gender identity disorder) is a classification used to describe persons who experience significant discontent with their biological sex and/or gender assigned at birth. Therapeutic options for gender dysphoria include behavioral and psychotherapies, hormonal treatments, and a number of surgeries used for gender reassignment. This proposed decision is only focusing on gender reassignment surgery.

B. Prevalence of Gender Dysphoria

Prevalence of gender dysphoria estimates have been reported by several investigators.

For estimates of transgender individuals in the U.S., we looked at several studies.

The Massachusetts Behavior Risk Factor Surveillance Survey (via telephone) (2007 and 2009) identified 0.5% individuals as transgender (Conron et al., 2012).

Derivative data obtained from the 2004 California Lesbian Gay Bisexual and Transgender (LGBT) Tobacco Survey (via telephone) and the 2009 California Health Interview Survey (CHIS) (via telephone) suggested the LGB population constitutes 3.2% of the California population and that transgender subjects constitute approximately 2% of the California LGBT population and 0.06% of the overall California population (Bye et al., 2005; CHIS 2009; Gates, 2011).

In a recent review of Medicare claims data, CMS estimated that in calendar year 2013 there were at least 4,098 transgender beneficiaries (less than 1% of the Medicare population) who utilized services paid for by Medicare, of which 90% had confirmatory diagnosis, billing codes, or evidence of a hormone therapy prescription. The Medicare transgender population is racially and ethnically diverse (e.g., 74% White, 15% African American) and spans the entire country. The following states have at least 100 transgender beneficiaries: California, Florida, Georgia, Illinois, Massachusetts, Michigan, Minnesota, New York, Pennsylvania, Ohio, Texas, Washington, and Wisconsin. Nearly 80% of transgender beneficiaries are under age 65, including approximately 23% ages 45-54. Of note, for the transgender population under age 65, the most prevalent chronic conditions were depression, major depressive affective disorder, and anxiety. Approximately 75% of transgender Medicare beneficiaries have been affected by depression, which is a disproportionately high amount compared to the Medicare population as a whole with 14% of Medicare fee-for-service beneficiaries suffering from the disease (CMS, *Chronic Conditions Among Medicare Beneficiaries*, 2012 at <https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/chronic-conditions/downloads/2012chartbook.pdf>). Based on the claims data, about 48% of transgender beneficiaries use hormone therapy, which are coverable under the Medicare Part D prescription drug benefit program (CMS Office of Minority Health (2015, June). New Directions in CMS Disparities Research: Sexual Orientation & Gender Identity. Paper presented at the Academy Health Annual Research Meeting, Minneapolis, Minnesota and Gay and Lesbian Medical Association Meeting, Portland, Oregon).

For international comparison purposes, recent estimates of transgender populations in other countries are similar to those in the United States. New Zealand researchers, using passport data, reported a prevalence of 0.0275% for male-to-female adults and 0.0044% female-to-male adults (6:1 ratio) (Veale, 2008). Researchers from a centers of transgender treatment and reassignment surgery in Belgium conducted a survey of regional plastic surgeons and reported a prevalence of 0.008% male-to-female and 0.003% female-to-male (ratio 2.7:1) surgically reassigned transsexuals in Belgium (De Cuypere et al., 2007). Swedish researchers, using national mandatory reporting data on those requesting reassignment surgery, reported secular changes over time in that the number of completed reassignment surgeries per application increased markedly in the 1990s; the male-to-female/female-to-male sex ratio changed from 1:1 to 2:1; the age of male-to-female and female-to-male applicants was initially similar, but increased by eight years for male-to-female applicants; and the proportion of foreign born applicants increased (Olsson, Moller 2003).

C. Interventions

Table 1 provides information about some of the types of therapeutic interventions for transgender individuals.

Table 1. Types of Therapeutic Intervention (May Not be Exhaustive)

Treatment Category	Male to Female	Female to Male
HORMONAL¹		
Core		
	Estrogens	Androgens Progestins/GnRH analogues for menses suppression as needed after 1 yr of androgens

Treatment Category	Male to Female	Female to Male
	Anti-androgens (e.g., spironolactone, 5- reductase blockers, androgen receptor blockers, GnRH analogues)	
SURGICAL^{2,3}		
Natal Internal Genital Removal	Orchidectomy (testes)	Hysterectomy (uterus) and Salpingo-oophorectomy (fallopian tubes + ovaries)
Natal External Genital Removal	Penectomy	NA
Breast Removal	NA	Mastectomy
Genital Reconstruction ²	Vaginoplasty Clitoroplasty Labiaplasty Urethrostomy	Metoidioplasty or Phalloplasty Inflatable/rigid penile prosthesis insertion Scrotal reconstruction

RH=gonadotropin releasing hormone NA=not applicable ?=possible =increased 2o=secondary

1—Bowman et al., 2012; Deutch, 2015; Elaut et al., 2010 Gooren et al., 2005 ,2013, and 2014; Heresova, 1986; Jacobeit, et al., 2009; Kronawitter et al., 2009; Meuller, 2010; Meyer et al., 1981; Pelusi et al., 2014; Schlatterer et al., 1998; Seal et al., 2012; Traish et al., 2010; Wierckx et al., 2011b, 2014; Williamson et al., 2010.

2—Revisions may be required. Kuhn et al., 2011.

3—Goddard et al., 2007a; Jain, Bradbeer, 2007; Selvaggi, Bellringer, 2011; Wroblewski et al., 2013.

III. History of Medicare Coverage

CMS does not currently have an NCD on gender reassignment surgery.

A. Current Request

On December 3, 2015, CMS accepted a formal complete request from a beneficiary to initiate a national coverage analysis (NCA) for gender reassignment surgery.

CMS opened this National Coverage Analysis (NCA) to thoroughly review the evidence to determine whether or not gender reassignment surgery may be covered nationally under the Medicare program.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For gender reassignment surgery, the following are statutes are applicable to coverage:

Under §1812 (Scope of Part A)

Under §1832 (Scope of Part B)

Under §1861(s) (Definition of Medical and Other Health Services)

Under §1861(s)(1) (Physicians' Services)

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Table 2: Timeline of Medicare Coverage Policy Actions for Gender Reassignment Surgery

Date	Action
August 1, 1989	The Health Care Financing Agency (HCFA; predecessor agency to CMS) published the initial NCD, titled "140.3, Transsexual Surgery" in the Federal Register. (54 Fed. Reg. 34,555, 34,572)
May 30, 2014	The HHS Departmental Appeals Board (DAB) determined that the NCD denying coverage for all transsexual surgery was not valid. As a result, MACs determined coverage on a case-by-case basis.
December 3, 2015	CMS accepts an external request to open an NCD. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
January 2, 2016	Initial comment period closed. CMS received 103 comments.

V. FDA Status

Surgical procedures *per se* are not subject to the Food and Drug Administration's (FDA) approval.

Inflatable penile prosthetic devices, rigid penile implants, testicular prosthetic implants, and breast implants have been approved/cleared by the FDA.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical question relevant to the coverage request can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer-reviewed medical journals. We considered articles cited by the requestor, in public comments, as well as those found by a CMS literature review. Citations are detailed below.

B. Literature Search Methods

CMS staff extensively searched for primary studies evaluating therapeutic interventions for gender dysphoria. There was particular emphasis on the various surgical interventions, but other treatments including hormone therapy, psychotherapy, psychiatric treatment, ancillary reproductive and gender modifying services, and post-operative surveillance services for natal sex organs were also included because of their serial and sometimes overlapping roles in patient management. The emphasis focused less on specific surgical techniques and more on functional outcomes unless specific techniques altered those types of outcomes.

The reviewed evidence included articles obtained by searching literature databases and technology review databases Case 7:16-cv-00108-Q Document 26 Filed 10/21/16 Page 600 of 919 PageID 1066 (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies. Systematic reviews were used to help locate some of the more obscure publications and abstracts.

Keywords used in the search included: Trans-sexual, transgender, gender identity disorder (syndrome), gender dysphoria and/or hormone therapy, gender surgery, genital surgery, gender reassignment (surgery), sex reassignment (surgery) AND/OR quality of life, satisfaction-regret, psychological function (diagnosis of mood disorders, psychopathology, personality disorders), employment status, relationships, other social function, suicide (attempts), mortality, sexual function, urinary function, and adverse events-reoperations. After the identification of germane publications, CMS also conducted searches on the specific psychometric instruments used by investigators.

Psychometric instruments are scientific tools used to measure individuals' mental capabilities and behavioral style. They are usually in the form of questionnaires that numerically capture responses. These tools are used to create a psychological profile that can address questions about a person's knowledge, abilities, attitudes and personality traits. In the evaluation of patients with gender dysphoria, it is important that both validity and reliability be assured in the construction of the tool (validity refers to how well the tool actually measures what it was designed to measure, or how well it reflects the reality it claims to represent, while reliability refers to how accurately results of the tool would be replicated in a second identical piece of research). That is because when evaluating patients with this condition most of the variables of interest (e.g., satisfaction, anxiety, depression) are latent in nature (not directly observed but are rather inferred) and difficult to quantify objectively.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than small, pilot studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important. Studies with fewer than 30 patients were reviewed and delineated, but excluded from the major analytic framework. Oral presentations, unpublished white papers, and case reports were excluded. Publications in languages other than English were excluded.

Included studies were limited to those with adult subjects. Review and discussion of the management of children and adolescents with the additional considerations of induced pubertal delay are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. The excluded duplicative publications are delineated.

CMS also searched Clinicaltrials.gov to identify relevant clinical trials. CMS looked at trial status including early termination, completed, and ongoing with sponsor update, and ongoing with estimated date of completion. Publications on completed trials were sought. The CMS internal search was limited to articles published prior to March 21, 2016. CMS reviewed results of clinical trials involving adult human subjects; to reports of prospective (e.g., blinded, non-blinded, cross sectional), partially prospective, retrospective longitudinal studies randomized meeting certain criteria.

C. Discussion of Evidence

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" CMS is interested in answering the following question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

The evidence reviewed is directed towards answering this question.

1. Internal Technology Assessment

When looking at the studies evaluating gender reassignment surgery for patients with gender dysphoria, we found an array of disparate research designs. Most of the studies were conducted in Europe. Only six studies took place in the U.S. (Ainsworth, Spiegel, 2010; Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006; Lawrence, 2006; Leinung et al., 2013). Most of the studies that evaluated gender dysphoria were descriptive in nature; few made inferences which may be applicable to the Medicare population.

CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions. CMS also explored the relative roles that psychological support, mental health care, cross-sex hormonal therapy, and the various gender reassignment related surgical procedures played in health outcomes.

CMS identified numerous publications related to gender reassignment surgery. A large number of these were case reports, case series with or without descriptive statistics, or studies with population sizes too small to conduct standard parametric statistical analyses. Others addressed issues of surgical technique.

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CMS identified and described 36 publications on gender reassignment surgery that included health outcomes. Because the various investigators at different times used different populations, studied sub-populations, studied different outcomes, or used different tools to study the same outcomes, not all study populations were unique. To reduce bias from over-lapping populations, only the latest or most germane publication(s) were described. Subsumed publications were delineated.

Of these 36 publications, two publications used different assessment tools on the same population, and, so for the purposes of evaluation, were classified as 1 study (Udeze et al., 2008; Megeri, Khoosal, 2007). For another publication, the complete manuscript could not be located despite an exhaustive search by the Library of Medicine (Barrett, 1998). This precluded adequate review, thus, it was not included. A total of 33 studies were reviewed (See Figure 1). Appendices C, D, and F include more detail of each study.

The publications covered a time span from 1979 to 2015. Over half of the studies were published after 2005.

Figure 1. Studies of Gender Reassignment Surgery (GRS)



ANOVA=Analysis of Variance Normative=Psychometric Tests with known normative for large populations

The studies in Figure 1 are categorized into 3 groups. The first group, depicted by the colored boxes (red, blue, and green), had explicit controls. There was a single randomized study. The remainder in the first group were observational studies. These were subdivided into longitudinal studies and cross-sectional studies. The second group, depicted by black boxes (starting with the surgery only populations box) consisted of surgical series. The third group, depicted by black boxes (starting with mixed population), was composed of mixed populations of patients not stratified by treatment and which included a spectrum of therapeutic interventions.

When looking at the totality of studies, they fell into the following research design groups:

a. Prospective, non-blinded, observational, cross-sectional studies with no concurrent controls

Ainsworth and Spiegel conducted a prospective, observational study using a cross-sectional design and a partially self-designed survey tool. The blind status is unknown. Treatment types served as the basis for controls.

The investigators, head and neck surgeons who provided facial feminization services, assessed perception of appearance and quality of life in male-to-female subjects with self-reported gender dysphoria. Patients could have received no therapeutic intervention, hormone therapy, reassignment surgery, and/or facial feminization surgery and an unrestricted length of transition. (Transition refers to the time when a transgender person begins to live as the gender with which they identify rather than the gender assigned at birth.) Criteria for the various types of interventions were not available because of the survey design of the study. Patients were recruited via website or at a 2007 health conference. Pre-specified controls to eliminate duplicate responders were not provided. The investigators employed a self-designed Likert-style facial feminization outcomes evaluation questionnaire and a "San Francisco 36" health questionnaire. No citations were provided for the latter. It appears to be the Short-form (SF) 36-version 2. Changes or differences considered to be biologically significant were not pre-specified. Power corrections for multiple comparisons were not provided.

The investigators reported that there were 247 participants. (The numbers of incomplete questionnaires was not reported.) Of the 247 participants, 25 (10.1%) received only primary sex trait reassignment surgery, 28 (11.3%) received facial surgery without primary sex trait reassignment surgery, 47 (19.0%) received both facial and primary sex trait reassignment surgery, and 147 (59.5%) received neither facial nor reassignment surgery. The mean age for each of these cohorts was: 50 (no standard deviation [S.D.]) only reassignment surgery, 51 (no S.D.) only facial surgery, 49 (no S.D.) both types of surgery, and 46 (no S.D.) (neither surgery). Of the surgical cohorts: 100% of those who had undergone primary sex trait reassignment surgery alone used hormone therapy, 86% of those who had undergone facial feminization used hormone therapy, and 98% of those who had undergone both primary sex trait reassignment surgery and facial feminization used hormone therapy. In contrast to the surgical cohorts, 66% of the "no surgery" cohort used hormonal therapy, and a large proportion (27%) had been in transition for less than 1 year.

The investigators reported higher scores on the facial outcomes evaluation in those who had undergone facial feminization. Scores of the surgical cohorts for the presumptive SF-36 comprehensive mental health domain did not differ from the general U.S. female population. Scores of the "no surgery" cohort for the comprehensive mental health domain were statistically lower than those of the general U.S. female population, but within 1 standard deviation of the normative mean. Mean scores of all the gender dysphoric cohorts for the comprehensive physical domain were statistically higher than those of the general female U.S. population, but were well within 1 standard deviation of the normative mean. Analyses of inter-cohort differences for the SF-36 results were not conducted. Although the investigators commented on the potential disproportionate impact of hormone therapy on outcomes and differences in the time in "transition", they did not conduct any statistical analyses to correct for putative confounding variables.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. *J Sex Med.* 2012 Mar;9(3):743-50. Epub 2011 Dec 21.

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Motmans et al., conducted a prospective, non-blinded, observational study using a cross-sectional design and a non-specific quality-of-life tool. No concurrent controls were used in this study. Quality of life in this Dutch-speaking population was assessed using the Dutch version of a SF-36 (normative data was used). Participants included subjects who were living in accordance with the preferred gender and who were from a single, unspecified, Belgian university specialty clinic. The Dutch version of the SF-36 questionnaire along with its normative data were used. Variables explored included employment, pension status, ability to work, being involved in a relationship. Also explored, was surgical reassignment surgery and the types of surgical interventions. Intragroup comparisons by transgender category were conducted, and the relationships between variables were assessed by analysis of variance (ANOVA) and correlations.

The age of the entire cohort (n=140) was 39.89±10.21 (female-to-male: 37.03±8.51; male-to-female: 42.26±10.39). Results of the analysis revealed that not all female-to-male patients underwent surgical reassignment surgery and, of those who did, not all underwent complete surgical reassignment. The numbers of female-to-male surgical interventions were: mastectomy 55, hysterectomy 55, metadoioplasty 8 (with 5 of these later having phalloplasty), phalloplasty 40, and implantation of a prosthetic erectile device 20. The frequencies of various male-to-female surgical interventions were: vaginoplasty 48, breast augmentation 39, thyroid cartilage reduction 17, facial feminization 14, and hair transplantation 3.

The final number of subjects with SF-36 scores was 103 (49 [47.6%] female-to-male; 54 [52.4%] male-to-female; ratio 1:1.1). For this measure, the scores for the vitality and mental health domains for the final female-to-male cohort (n= 49 and not limited to those having undergone some element of reassignment surgery) were statistically lower: 60.61±18.16 versus 71.9±18.31 and 71.51±16.40 versus 79.3±16.4 respectively. Scores were not different from the normative data for Dutch women: vitality: 64.3±19.7 or mental health 73.7±18.2. None of the domains of the SF-36 for the final male-to-female cohort (n=54 and not limited to those having undergone some element of reassignment surgery) were statistically different from the normative data for Dutch women.

Analysis of variance indicated that quality-of-life as measured by the SF-36 did not differ by whether female-to-male patients had undergone genital surgery (metadoidoplasty or phalloplasty) or not. Also, ANOVA indicated that quality-of-life as measured by the SF-36 did not differ by whether male-to-female patients had undergone either breast augmentation or genital surgery (vaginoplasty) or not.

Whether there is overlap with the Ghent populations studied by Heylens et al., Weyers et al., or Wierckx et al. is unknown.

Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med.* 2009 Mar;6(3):752-60. Epub 2008 Nov 17.

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Weyers et al. 2009 conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments including a self-reported quality of life and self-rated quality of life tool (using normative data) along with 2 self-designed tools.

The investigators assessed general quality of life, sexual function, and body image from the prior 4 weeks in Dutch-speaking male-to-female patients with gender dysphoria who attended a single-center, specialized, comprehensive care university clinic. Investigators used the Dutch version of the SF-36 and results were compared to normative data from Dutch women and U.S. women. The 19 items of the Dutch version of the Female Sexual Function Index (FSFI) were used to measure sexual desire, function, and satisfaction. A self-designed 7 question visual analog scale (VAS) was used to measure satisfaction with gender related body traits and appearance perception by self and others. A self-designed survey measured a broad variety of questions regarding personal medical history, familial medical history, relationships, importance of sex, sexual orientation, gynecologic care, level of regret, and other health concerns. For this study, hormone levels were also obtained.

The study consisted of 50 participants. Analysis of the data revealed that the patient's average age was 43.1 ± 10.4 years, and all of the patients had vaginoplasty. This same population also had undergone additional feminization surgical procedures (breast augmentation 96.0%, facial feminization 36.0%, vocal cord surgery 40.0%, and cricoid cartilage reduction 30.0%). A total of two (4.0%) participants reported "sometimes" regretting reassignment surgery and 23 (46.0%) were not in a relationship. For the cohort, estradiol, testosterone, and sex hormone binding globulin levels were in the expected range for the reassigned gender. The SF-36 survey revealed that the subscale scores of the participants did not differ substantively from those of Dutch and U.S. women. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

The total FSFI score was 16.95 ± 10.04 out of a maximal 36. The FSFI scores averaged 2.8 (6 point maximum): satisfaction 3.46 ± 1.57 , desire 3.12 ± 1.47 , arousal 2.95 ± 2.17 , lubrication 2.39 ± 2.29 , orgasm 2.82 ± 2.29 , and pain 2.21 ± 2.46 . Though these numbers were reported in the study, data on test population controls were not provided. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

A *post hoc* exploration of the data was performed that revealed the following: perceived improvement in general health status was greater in the subset that had undergone reassignment surgery within the last year; sexual orientation impacted the likelihood of being in a relationship; SF-36 scores for vitality, social functioning, and mental health were nominally better for those in relationships, but that overall SF-36 scores did not differ by relationship status; sexual orientation and being in a relationship impacted FSFI scores; and reported sexual function was higher in those with higher satisfaction with regards to their appearance.

Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med.* 2011 Dec;8(12):3379-88. Epub 2011 Jun 23.

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Wierckx et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments (a non-specific quality of life tool with reported normative data along with 3 self-designed tools). The investigators assessed general quality of life, sexual relationships, and surgical complications in Dutch-speaking female-to-male patients with gender dysphoria who attended a single-center, specialized, comprehensive care, university clinic. Investigators used the Dutch version of the SF-36 with 36 questions, 8 subscales, and 2 domains evaluating physical and mental health. Results were compared to normative data from Dutch women and Dutch men. Self-designed questionnaires to evaluate aspects of medical history, sexual functioning (there were separate versions for those with and without partners), and surgical results were also used. The Likert-style format was used for many of the questions.

A total of 79 female-to-male patients with gender dysphoria had undergone reassignment surgery were contacted; however, ultimately, 47 (59.5%) chose to participate. Three additional patients were recruited by other patients. One of the 50 participants was later excluded for undergoing reassignment surgery within the 1 year window. The age of patients was: 30 ± 8.2 years (range 16 to 49) at the time of reassignment surgery and 37.1 ± 8.2 years (range 22 to 54) at the time of follow-up. The time since hysterectomy, oophorectomy, and mastectomy was 8 years (range 2 to 22). The patient population had undergone additional surgical procedures: metoidioplasty (n=9; 18.4%), phalloplasty (n=8 after metoidioplasty, 38 directly; 93.9% total), and implantation of erectile prosthetic device (n=32; 65.3%). All had started hormonal therapy at least 2 years prior to surgery and continued to use androgens.

The SF-36 survey was completed by 47 (95.9%) participants. The "Vitality" and the "Mental Health" scales were lower than the Dutch male population: 62.1 ± 20.7 versus 71.9 ± 18.3 and 72.6 ± 19.2 versus 79.3 ± 16.4 respectively. These subscale scores were equivalent to the mean scores of the Dutch women.

None of the participants were dissatisfied with their hysterectomy-oophorectomy procedures; 4.1% were dissatisfied with their mastectomies because of extensive scarring; and 2.2% were dissatisfied with their phalloplasties. Of the participants, 17.9% were dissatisfied with the implantation of an erectile prosthetic device; 25 (51.0%) reported at least one post-operative complication associated with phalloplasty (e.g., infection, urethrostenosis, or fistula formation); 16 (50.0% of the 32 with an erectile prosthetic device) reported at least one post-operative complication associated with implantation of an erectile prosthetic (e.g., infection, leakage, incorrect positioning, or lack of function).

A total of 18 (36.7%) participants were not in a relationship; 12.2% reported the inability to achieve orgasm with self-stimulation less than half the time; 12.2% did not respond to the question. Of those with participants with partners, 28.5% reported the inability to achieve orgasm with intercourse less than half the time and 9.7% did not respond to this question. Also, 61.3% of those with partners reported (a) no sexual activities (19.4%) or (b) activities once or twice monthly (41.9%), and there were 12.9% who declined to answer.

Post hoc assessments suggested that being in relationship or having undergone phalloplasty did not impact the scores of the SF-36 domains. Also this assessment suggested that for patients in a relationship, sexual satisfaction was related to "Vitality" scores. Finally this assessment suggested a relationship between sexual satisfaction and more frequent orgasm and pleasure with the partner.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun;66(4):371-2. PMID: 22624747.

Salvador et al. conducted a prospective, non-blinded, observational study using a cross-sectional design (albeit over an extended time interval) and a self-designed quality of life tool. The investigators assessed regret, sexual function, partnerships, and family relationships in patients who had undergone gender reassignment surgery at least 24 months prior.

Out of the 243 enrolled in the clinic over a 10 year interval, 52 patients agreed to participate in the study. The age at follow-up was 36.3 ± 8.9 (range 15-58) years with the time to follow-up being 3.8 ± 1.7 (2-7) years. A total of 46 participants reported pleasurable neo-vaginal sex and post-surgical improvement in the quality of their sexual experience. The quality of sexual intercourse was rated as satisfactory to excellent, average, unsatisfactory, or not applicable in the absence of sexual contact by 84.6%, 9.6%, 1.9%, and 3.8% respectively. Of the participants, 78.8% reported greater ease in initiating and maintaining relationships; 65.4% reported having a partner; 67.3% reported increased frequency of intercourse; 36.8% reported improved familial relationships. No patient reported regret over reassignment surgery. The authors did not provide information about incomplete questionnaires.

Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304.

Blanchard et al. conducted a prospective, non-blinded, cross-sectional study using a self-designed questionnaire and a non-specific psychological symptom assessment with normative data. The investigators assessed social adjustment and psychopathology in patients with gender dysphoria and who were at least 1 year post gender reassignment surgery. Reassignment surgery was defined as either vaginoplasty or mastectomy/construction of male chest contour with or without nipple transplants, but did not preclude additional procedures. Partner preference was determined using the Modified Androphilia-Gynephilia Index, and the nature and extent of any psychopathology was determined with the Symptom Check List 90-Revised (SCL-90R).

Of the 294 patients (111 natal females and 183 natal males, ratio: 1:1.65) initially evaluated, 79 patients participated in the study (38 female-to-male; 32 male-to-female with male partner preference; 9 male-to-female with female partner preference). The respective mean ages for these 3 groups were 32.6, 33.2, and 47.7 years with the last group being older statistically ($p=0.01$). Additional surgeries in female-to-male patients included: oophorectomy/hysterectomy 92.1% and phalloplasty 7.9%. Additional procedures in male-to-female patients with male partner preference included facial hair electrolysis 62.5% and breast implantation 53.1%. Additional procedures in male-to-female patients with female partner preference included facial hair electrolysis 100% and breast implantation 33.3%. The time between reassignment surgery and questionnaire completion did not differ by group.

Of participants, 63.2% of female-to-male patients cohabitated with partners of their natal gender. 46.9% of male-to-female patients with male partner preference cohabitated with partners of their natal gender; 93.7% reported that they would definitely undergo reassignment surgery again. The remaining 6.3% (1 female-to-male; 1 male-to-female with male partner preference; 3 male-to-female with female partner preference) indicated that they probably would undertake the surgery again. *Post hoc* analysis suggested that the more ambivalent responders had more recently undergone surgery. Of responders, 98.7% indicated that they preferred life in the reassigned gender. The one ambivalent subject was a skilled and well compensated tradesperson who was unable to return to work in her male dominated occupation.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. Singapore Med J. 1993 Dec;34(6):515-7.

Tsoi conducted a prospective, non-blinded, observational study using a cross-sectional design and a self-designed quality of life tool. The investigators assessed overall life satisfaction, employment, partner status, and sexual function in gender-reassigned persons who had undergone gender reassignment surgery between 1972 and 1988 inclusive and who were approximately 2 to 5 years post-surgery. Acceptance criteria for surgery included good physical health, good mental health, absence of heterosexual tendencies, willingness to undergo hormonal therapy for ≥ 6 months, and willingness to function in the life of the desired gender for ≥ 6 months. Tsoi also undertook retrospective identification of variables that could predict outcomes.

The size of the pool of available patients was not identified. Of the 81 participants, 36 were female-to-male (44.4%) and 45 were male-to-female (55.6%) (ratio 1:1.25).

The mean ages at the time of the initial visit and operation were: female-to-male 25.4 ± 4.4 (range 14-36) and 27.4 ± 4.0 ; (range 14-36); male-to-female 22.9 ± 4.6 (range 14-36) and 24.7 ± 4.3 (14-36) years respectively. Of all participants, 14.8% were under age 20 at the time of the initial visit. All were at least 20 at the time of gender reassignment surgery. The reported age of onset was 8.6 years for female-to-male patients and 8.7 years for male-to-female patients.

All participants reported dressing without difficulty in the reassigned gender; 95% of patients reported good or satisfactory adjustment in employment and income status; 72% reported good or satisfactory adjustment in relationships with partners. Although the quality of life tool was self-designed, 81% reported good or satisfactory adjustment to their new gender, and 63% reported good or acceptable satisfaction with sexual activity. Of the female-to-male patients, 39% reported good or acceptable satisfaction with sex organ function in comparison to 91% of male-to-female patients ($p < 0.001$). (The author reported that a fully functioning neo-phallus could not be constructed at the time.) The age of non-intercourse sexual activity was the only predictor of an improved outcome.

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012 May;37(5):662-70. Epub 2011 Sep 19.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a cross-sectional design and non-specific psychiatric distress tools in Spain. The investigators assessed anxiety and depression in patients with gender dysphoria who attended a single-center specialty clinic with comprehensive endocrine, psychological, psychiatric, and surgical care. The clinic employed World Professional Association for Transgender Health (WPATH) guidelines. Patients were required to have met diagnostic criteria during evaluations by 2 experts. Investigators used the Hospital Anxiety and Depression Scale (HADS) and the Social Anxiety and Distress Scale (SADS) instruments. The SADS total score ranges from 0 to 28, with higher scores indicative of more anxiety. English language normative values are 9.1 ± 8.0 . HAD-anxiety and HAD-depression total score ranges from 0 to 21, with higher scores indicative of more pathology. Scores less than 8 are normal. ANOVA was used to explore effects of hormone and surgical treatment.

Of the 200 consecutively selected patients recruited, 187 (93.5% of recruited) were included in the final study population. Of the final study population, 74 (39.6%) were female-to-male patients; 113 (60.4%) were male-to-female patients (ratio 1:1.5); and 120 (64.2%) were using hormones. Of those using hormones, 36 (30.0%) were female-to-male; 84 (70.0%) were male-to-female (ratio 1:2.3). The mean age was 29.87 ± 9.15 (range 15-61). The current age of patients using hormones was 33.6 ± 9.1 ($n=120$) and older than the age of patients without hormone treatment (25.9 ± 7.5) ($p=0.001$). The age at hormone initiation, however, was 24.6 ± 8.1 .

Of those who had undergone reassignment surgery, 29 (36.7%) were female-to-male; 50 (63.3%) were male-to-female; ratio 1:1.7. The number of patients not on hormones and who had undergone at least 1 gender-related surgical procedure (genital or non-genital) was small ($n=2$). The number of female-to-male patients on hormones who had undergone such surgery (mastectomy, hysterectomy, or phalloplasty) was 28 (77.8%). The number of male-to-female patients on hormones who had undergone such surgery (mammoplasty, facial feminization, buttock feminization, vaginoplasty, orchiectomy, and vocal feminization (thyroid chondroplasty) was 49 (58.3%).

Analysis of the data revealed that although the mean scores HAD-Anxiety, HAD-Depression, and SADS were statistically lower (better) in those on hormone therapy than in those not on hormone therapy, the mean scores for HAD-Depression and SADS were in the normal range for gender dysphoric patients not using hormones. The HAD-Anxiety score was borderline elevated and consistent with a possible mood disorder in patients not using hormones. The mean scores for HAD-Anxiety, HAD-Depression, and SADS were in the normal range for gender dysphoric patients using hormones. ANOVA revealed that results did not differ by whether the patient had undergone a gender related surgical procedure or not.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-76. Epub 2013 Aug 13.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a non-specific quality of life tool. There were no formal controls for this mixed population \pm non-genital reassignment surgery. The investigators assessed quality of life in the context of culture in patients with gender dysphoria who were from a single-center, specialty and gender identity clinic. The clinic used WPATH guidelines. Patients were required to have met diagnostic criteria during evaluations by both a psychologist and psychiatrist. Patients could have undergone non-genital surgeries, but NOT genital reassignment surgeries (e.g., orchiectomy, vaginoplasty, or phalloplasty).

The Spanish version of the World Health Organization Quality of Life-Abbreviated version of the WHOQOL-100 (WHOQOL-BREF) was used to evaluate quality-of-life, which has 4 domains (environmental, physical, psychological, and social) and 2 general questions. Family dynamics were assessed with the Spanish version of the Family Adaptability, Partnership Growth, Affection, and Resolve (APGAR) test. Regression analysis was used to explore effects of surgical treatment.

Of the 277 patients recruited, 260 (93.9%) agreed to participate. Of this number, 193 were included in the study (the mean age of this group was 31.2 ± 9.9 (range 16-67)). Of these, 74 (38.3%) were female-to-male patients; 119 (61.7%) were male-to-female patients; ratio 1:1.6. 120 (62.2%) were on hormone therapy; 29 (39.2%) of female-to-male patients had undergone at least 1 non-genital, surgical procedure (hysterectomy $n=19$ (25.7%); mastectomy $n=29$ (39.2%)); 51 (42.9%) of male-to-female patients had undergone at least 1 non-genital surgical procedure with mammoplasty augmentation being the most common procedure, $n=47$ (39.5%), followed by facial feminization, $n=11$ (9.2%), buttocks feminization, $n=9$ (7.6%), and vocal feminization (thyroid chondroplasty), $n=2$ (1.7%).

WHOQOL-BREF domain scores for gender dysphoric patients with and without non-genital surgery were: "Environmental" 58.81 ± 14.89 (range 12.50-96.88), "Physical" 63.51 ± 17.79 (range 14.29-100), "Psychological" 56.09 ± 16.27 (range 16.67-56.09), "Social" 60.35 ± 21.88 (range 8.33-100), and "Global QOL and Health" 55.44 ± 27.18 (range 0-100). The mean APGAR family score was 7.23 ± 2.86 (range 0-10).

Regression analysis, which was used to assess the relative importance of various factors to WHOQOL-BREF domains and general questions, revealed that family support was an important element for all 4 domains and the general health and quality-of-life questions. Hormone therapy was an important element for the general questions and for all of the domains except "Environmental." Having undergone non-genital reassignment surgery, like age, educational levels, and partnership status, did not impact domain and general question results related to quality of life.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. Br J Psychiatry. 1988 Apr;152:550-3.

psychological tests (1 with some normative data). Concurrent controls were used in this study design. The investigator assessed the clinical and psychosocial data of 24 transgender dysphoric patients at various stages of management, (i.e., under evaluation, using cross-sex hormones, or post reassignment surgery [6 months to 2 years]) were matched by age of cross-dressing onset, childhood neuroticism, personal psychiatric history, and family psychiatric history. Both a psychologist and psychiatrist conducted assessments. The instruments used were the Crown Crisp Experiential Index (CCEI) for psychoneurotic symptoms and the Bem Sex Role Inventory. ANOVA was used to identify differences between the three treatment cohorts.

For each cohort, investigators recruited 50 male-to-female patients. The mean ages of the three cohorts were as follows: undergoing evaluation: mean age 34 years; wait-listed: mean age 35 years; and post-operative: mean age 37 years. Of the groups under evaluation or postsurgical, 16% (8 each) were unemployed; 8% of the waited listed patients were unemployed. For the cohorts, 22% of those under evaluation, 24% of those on hormone treatment only, and 30% of those post-surgery had prior psychiatric histories, and 24%, 24%, and 14% of the same respective cohorts had a history of attempted suicide. More than 30% of patients in each cohort had a first degree relative with a history of psychiatric disease.

The scores for the individual CCEI domains for depression and somatic anxiety were relatively higher (worse) for patients under evaluation than those on hormone treatment alone. The scores for all of the individual CCEI domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessiveness) were lower in the post-operative cohort than in the other 2 cohorts.

The Bem Sex Role Inventory masculinity score for the combined cohorts was lower than for North American norms for either men or women. The femininity score for the combined cohorts was higher than for North American norms for either men or women. Those who were undergoing evaluation had the most divergent scores from North American norms and from the other treatment cohorts. Absolute differences were small. All scores of gender dysphoric patients averaged between 3.95 and 5.33 on a 7 point scale while the normative scores averaged between 4.59 and 5.12.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg. 1997 Mar;31(1):39-45.

Eldh et al. conducted a non-blinded, observational study using a prospective cross-sectional design with a self-designed questionnaire and retrospective acquisition of pre-operative data. The investigators assessed economic circumstances, family status, satisfaction with surgical results, and sexual function in patients who had undergone gender reassignment surgery. Of the 175 patients who underwent reassignment surgery in Sweden, 90 responded. Of this number, 50 were female-to-male and 40 were male-to-female (ratio: 1:0.8). Patients reportedly were generally satisfied with the appearance of the reconstructed genitalia (no numbers provided). Of the patients who had undergone surgery prior to 1986, seven (14%) were dissatisfied with shape or size of the neo-phallus; 8 (16%) declined comment. There were 14 (35%), with 12 having surgery prior to 1986 and two between 1986 and 1995 inclusive, were moderately satisfied because of insufficient vaginal volume; 8 (20%) declined comment. A neo-clitoris was not constructed until the later surgical cohort. Three of 33 reported no sensation or no sexual sensation. Eight had difficulties comprehending the question and did not respond.

A total of nine (18%) patients had doubts about their gender orientation; 9 (28%) declined to answer the question; 44 (27 [61.3%] female-to-male and 17 [38.6%] male-to-female) were unmarried or without a steady partner; 19 (38.0%) female-to-male patients reported the absence of a sex life (28.0% declined to answer this particular question); 15 (30%) male-to-female reported dissatisfaction with their sex lives. Additionally, 3 (6.0%) reported absence of sexual activity post-operatively. Ten (11.1%) were dissatisfied with their life situation (17.8% declined to answer this question). The study found that 2 female-to-male patients and 2 male-to-female patients regretted their reassignment surgery and continued to live as the natal gender, and two patients attempted suicide.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005 Mar;58(3):259-61.

Hepp et al. conducted a prospective, non-blinded, observational study using a cross-sectional design. There was some acquisition of retrospective data. The investigators assessed current and lifetime psychiatry co-morbidity using structured interviews for diagnosis of Axis 1 disorders (clinical syndromes) and Axis 2 disorders (developmental or personality disorders) and HADS for dimensional evaluation of anxiety and depression. Statistical description of the cohort and intra-group comparisons was performed. Continuous variables were compared using t-tests and ANOVA.

A total of 31 patients with gender dysphoria participated in the study: 11 (35.5%) female-to-male; 20 (64.5%) male-to-female (ratio 1:1.8). The overall mean age was 32.2 ± 10.3 . Of the participants, seven had undergone reassignment surgery, 10 pre-surgical patients had been prescribed hormone therapy, and 14 pre-surgical patients had not been prescribed hormone therapy. Forty five and one half percent of female-to-male and 20% of male-to-female patients did not carry a lifetime diagnosis of an Axis 1 condition. Sixty three and six tenths percent of female-to-male and 60% of male-to-female patients did not carry a current diagnosis of an Axis 1 condition. Lifetime diagnosis of substance abuse and mood disorder were more common in male-to-female patients (50% and 55% respectively) than female-to-male patients (36.4% and 27.3% respectively). Current diagnosis of substance abuse and mood disorder were present in male-to-female patients (15% and 20% respectively) and absent in female-to-male patients. One or more personality disorders were identified 41.9%, but whether this was a current or lifetime condition was not specified. Of the patients, five (16.1%) had a Cluster A personality disorder (paranoid-schizoid), seven (22.6%) had a Cluster B personality disorder (borderline, anti-social, histrionic, narcissistic), six (19.4%) had a Cluster C personality disorder (avoidant, dependent, obsessive-compulsive), and two (6.5%) were not otherwise classified.

The HADS test revealed non-pathologic results for depression (female-to-male: 6.64 ± 5.03 ; male-to-female: 6.58 ± 4.21) and borderline results for anxiety (female-to-male: 7.09 ± 5.11 ; male-to-female: 7.74 ± 6.13 , where a result of 7-10 = possible disorder). There were no differences by natal gender. HADS scores were missing for at least 1 person. The investigators reported a trend for less anxiety and depression as measured by HADS in the patients who had undergone surgery.

b. Prospective, non-blinded, observational, cross-sectional studies with patients serving as their own controls

Rakic Z, Starcevic V, Maric J, Kelin K. *The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes.* Arch Sex Behav. 1996 Oct;25(5):515-25.

Rakic et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and an investigator-designed quality of life tool that asked longitudinal (pre- and post-treatment) questions. Patients served as their own controls. The authors state that the study was not designed to assess the predictors of poor outcomes.

The investigators assessed global satisfaction, body image, relationships, employment status, and sexual function in patients with gender dysphoria who underwent reassignment surgery between 1989 and 1993 and were at least 6 months post-operative. The criteria to qualify for gender surgery were delineated (1985 standards from the Harry Benjamin International Gender Dysphoria Association) and included cross-gender behavior for at least 1 year. The questionnaire consisted of 10 questions using yes/no answers or Likert-type scales. Findings were descriptive without statistical analysis. As such, changes or differences considered to be biologically significant were not pre-specified, and there were no adjustments for multiple comparisons.

Of the 38 patients who had undergone reassignment surgery, 32 participated in the study 10 (31.2%) female-to-male and 22 (68.8%) male-to-female (ratio 1:2.2). The duration of follow-up was 21.8 ± 13.4 months (range 6 months to 4 years). The age was female-to-male 27.8 ± 5.2 (range 23-37) and male-to-female 26.4 ± 7.8 (range 19-47).

Using an investigator-designed quality of life tool, all patients reported satisfaction with having undergone the surgery. Of the total participants, four (12.5%) (all male-to-female) and 8 (25%) (87.5% male-to-female) reported complete dissatisfaction or partial satisfaction with their appearance. Regarding relationships, 80% of female-to-male and 100% of male-to-female patients were dissatisfied with their relationships with others prior to surgery; whereas, no female-to-male patients and 18.1% of male-to-female patients were dissatisfied with relationships after surgery. Regarding sexual partners, 60% of female-to-male and 72.7% of male-to-female patients reported not having a sexual partner prior to surgery; whereas, 20% of female-to-male patients and 27.3% of male-to-female patients did not have a sexual partner after surgery. Of those with partners at each time interval, 100% of female-to-male and 50% of male-to-female patients reported not experiencing orgasm prior to surgery; whereas, 75% of female-to-male and 37.5% of male-to-female patients reported not experiencing orgasm after surgery. Fifty percent of female-to-male and 54.5% of male-to-female patients reported being either unemployed or not being a student full-time prior to surgery. After surgery, no female-to-male patients and 7 (31.8%) male-to-female patients reported being either unemployed or not being a student full-time. The change was due to student status. Six (60%) of female-to-male patients and 15 (68.2%) of male-to-female patients reported being unemployed before and after surgery.

c. Prospective, non-blinded, observational, cross-sectional studies with controls

Wolfradt and Neumann conducted a controlled, prospective, non-blinded, observational study using a cross-sectional design. The investigators assessed aspects of personality in male-to-female patients who had undergone vocal cord surgery for voice feminization and in healthy volunteers from the region. The patients had undergone gender reassignment surgery 1 to 5 years prior to voice surgery. The volunteers were matched by age and occupation. The primary hypothesis was that depersonalization, with the sense of being detached from one's body or mental processes, would be more common in male-to-female patients with gender dysphoria. German versions of the Scale for Depersonalization Experiences (SDPE), the Body Image Questionnaire (BIQ), a Gender Identity Trait Scale (GIS), and the Self-Esteem Scale (SES) were used in addition to a question regarding global satisfaction. Three of the assessments used a 5 point scale (BIQ, GIS, and SDPE) for questions. One used a 4 point scale (SES). Another used a 7 point scale (global satisfaction). The study consisted of 30 male-to-female patients, 30 healthy female volunteers, and 30 healthy male volunteers. The mean age of study participants was 43 (range 29-67).

Results of the study revealed that there were no differences between the three groups for the mean scores of measures assessing depersonalization, global satisfaction, the integration of masculine traits, and body-image-rejected (subset). Also, the sense of femininity was equivalent for male-to-female patients and female controls and higher than that in male controls. The levels of self-esteem and body image-dynamic (subset) were equivalent for male-to-female patients and male controls and higher than that in female controls, and none of the numeric differences between means exceeded 0.61 units.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. J Nerv Ment Dis. 1985 Jun;173(6):358-65. (United States study)

Beatrice conducted a prospective, non-blinded, observational study using a cross-sectional design and control cohorts in the U.S. The investigator assessed psychological adjustment and functioning (self-acceptance) in male-to-female patients with gender dysphoria (with and without gender reassignment surgery [GRS]), transvestites from two university specialty clinics, and self-identified heterosexual males recruited from the same two universities. The criteria to qualify for the study included being known to the clinic for at least one year, cross-dressing for at least one year without arrest, attendance at 10 or more therapy sessions, emotionally self-supporting, and financially capable of payment for reassignment surgery, and all of these criteria were met by the pre-operative cohort as well as the post-operative cohort. The cohorts were matched to the post-operative cohort (age, educational level, income, ethnicity, and prior heterosexual object choice). The post-operative cohort was selected not on the basis of population representation, but on the basis of demographic feasibility for a small study. The instruments used were the Minnesota Multiphasic Personality Inventory (MMPI) and the Tennessee Self-Concept Scale (TSCS). Changes or differences considered to be biologically significant were not pre-specified.

Of the initial 54 recruits, ten subjects were left in each of the cohorts because of exclusions identified due to demographic factors. The mean age of each cohort were as follows: pre-operative gender dysphoric patients 32.5 (range 27-42) years, postoperative patients 35.1 (30-43) years old, transvestite 32.5 (29-37) years old, and heterosexual male 32.9 (28-38) years old. All were Caucasian. The mean age for cross-dressing in pre-operative patients (6.4 years) and post-operative patients (5.8 years) was significantly lower than for transvestites (11.8 years).

The scores for self-acceptance did not differ by diagnostic category or surgical status as measured by the TSCS instrument. As measured by the T-scored MMPI instrument (50 ± 10), levels of paranoia and schizophrenia were higher for post-operative (GRS) patients (63.0 and 68.8) than transvestites (55.6 and 59.6) and heterosexual males (56.2 and 51.6). Levels of schizophrenia were higher for pre-operative patients (65.1) than heterosexual males (51.6). There were no differences between patients with gender dysphoria by surgical status. Scores for the Masculine-Feminine domain were equivalent in those with transvestitism and gender dysphoria with or without surgery, but higher than in heterosexual males. The analysis revealed that despite the high level of socio-economic functioning in these highly selected subjects, the MMPI profiles based on the categories with the highest scores were notable for antisocial personality, emotionally unstable personality, and possible manic psychosis in the pre-operative GRS patients and for paranoid personality, paranoid schizophrenia, and schizoid personality in the post-operative GRS patients. By contrast, the same MMPI profiling in heterosexual males and transvestites was notable for the absence of psychological dysfunction.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology. 2008;41(2):96-100. Epub 2007 Nov 23.

Kraemer et al. conducted a prospective, non-blinded, observational study using a cross-sectional design comparing pre-and post-surgical cohorts. The investigators assessed body image, and patients were required to meet DSM III or DSM IV criteria as applicable to the time of entry into the clinic. Post-surgical patients were from a long-term study group (Hepp et al., 2002). Pre-surgical patients were recent consecutive referrals. The assessment tool was the Fragebogen zur Beurteilung des eigenen Körpers (FBek) which contained 3 domains.

There were 23 pre-operative patients: 7 (30.4%) female-to-male and 16 (69.6%) male-to-female (ratio 1:2.3). There were 22 post-operative patients: 8 (36.4 %) female-to-male and 14 (63.6%) male-to-female (ratio 1:1.8). The mean ages of the cohorts were as follows: pre-operative 33.0 ± 11.3 years; post-operative 38.2 ± 9.0 years. The mean duration after reassignment surgery was 51 ± 25 months (range 5-96).

The pre-operative groups had statistically higher insecurity scores compared to normative data for the natal sex: female-to-male 9.0 ± 3.8 versus 5.1 ± 3.7 ; male-to-female 8.1 ± 4.5 versus 4.7 ± 3.1 as well as statistically lower self-confidence in one's attractiveness: female-to-male 3.1 ± 2.9 versus 8.9 ± 3.1 ; male-to-female 7.0 ± 2.9 vs 9.5 ± 2.6 . Scores for insecurity and self-confidence in the post-operative cohort were not inferior to the normative values. Insecurity decreased statistically from 9.0 ± 3.8 in the female-to-male pre-operative cohort and from 8.1 ± 4.5 in the male-to-female pre-operative cohort to 4.4 ± 3.8 and 3.4 ± 2.3 in the respective post-operative cohorts. Self-confidence increased statistically from 3.1 ± 2.9 in the female-to-male pre-operative cohort and 7.0 ± 2.9 male-to-female pre-operative cohort to 9.29 ± 1.98 and 10.29 ± 2.0 in the respective post-operative cohorts.

d. Prospective, non-blinded, observational, cross-sectional studies with semi-matched controls

Kuhn et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and semi-matched control cohort. The investigators assessed global satisfaction in patients who were from gynecology and endocrinology clinics, and who had undergone some aspect of gender reassignment surgery in the distant past, but were still receiving cross-sex hormones from the clinic. The quality-of-life assessment tools included a VAS and the King's Health Questionnaire (KHQ) with its eight domains including one for incontinence. The KHQ questionnaire and the numerical change/difference required for clinical significance (≥ 5 points in a given domain, with higher scores being more pathologic) were included in the publication. Twenty healthy female controls from the medical staff who had previously undergone an abdominal or pelvic surgery were partially matched by age and body mass index (BMI), but not sex.

Of the 55 participants, three (5.4%) were female-to-male and 52 (94.5%) were male-to-female (ratio 1:17.3). Reassignment surgery had been conducted 8 to 23 years earlier (median 15 years). The median age of the patients at the time of the study was 51 years (range 39-62 years). The patients had undergone a median of 9 surgical procedures in comparison to the 2 undergone by controls. Patients were less likely to be married (23.6% versus 65%; $p=0.002$), and partnership status was unknown in 5 patients. The scores of VAS global satisfaction (maximal score 8) were lower for surgically reassigned patients (4.49 ± 0.1 SEM) than controls (7.35 ± 0.26 SEM) ($p < 0.0001$).

There were statistically and biologically significant differences for 4 of the 8 domains between the patients and controls: physical limitation: 37.6 ± 2.3 versus 20.9 ± 1.9 ($p < 0.0001$), personal limitation: 20.9 ± 1.9 versus 11.6 ± 0.4 ($p < 0.001$), role limitation: 27.8 ± 2.4 versus 34.6 ± 1.7 ($p < 0.5$), and general health: 31.7 ± 2.2 versus 41.0 ± 2.3 ($p < 0.02$). Information as to whether a high or low score was positive for the various domains was not provided. Wording from the abstract suggests that these 4 differences all reflected lower quality-of-life.

e. Prospective, blinded, observational, cross-sectional studies with no concurrent controls

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int*. 2014 Nov 21;111(47):795-801.

Hess et al. conducted a prospective, blinded, observational study using a cross-sectional design and a self-designed questionnaire. The investigators assessed post-operative satisfaction in male-to-female patients with gender dysphoria who were followed in a urology specialty clinic. Patients had met the ICD-10 diagnostic criteria, undergone gender reassignment surgeries including penile inversion vaginoplasty, and a Likert-style questionnaire survey with 11 elements. Descriptive statistics were provided.

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There were 254 consecutive eligible patients who had undergone surgery between 2004 and 2010 identified and sent surveys, of whom 110 (43.3%) responded. Of the 110 patients, 13 (11.8%) reported dissatisfaction with outward appearance and 16 (13.4%) did not respond; three (2.5%) reported dissatisfaction with surgical aesthetics and 25 (21.0%) did not respond; eight (6.7%) reported dissatisfaction with functional outcomes of the surgery and 26 (21.8%) did not respond; 16 (13.4%) reported they could not achieve orgasm and 28 (23.5%) did not respond; four (3.4%) reported feeling completely male/more male than female and 28 (23.5%) did not respond; six (5.0%) reported not feeling accepted as a woman, two (1.7%) did not understand the question, and 17 (14.3%) did not respond; and 16 (13.4%) reported that life was harder and 24 (20.2%) did not respond.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. (United States study)

Lawrence conducted a prospective, blinded observational study using a cross-sectional design and a partially self-designed quality of life tool using yes/no questions or Likert scales. The investigator assessed sexual function, urinary function, and other pre/post-operative complications in patients who underwent male-to-female gender reassignment surgery. Questions addressed core reassignment surgery (neo-vagina and sensate neo-clitoris) and related reassignment surgery (labiaplasty, urethral meatus revision, vaginal deepening/widening, and other procedures), use of electrolysis, and use of hormones.

Questionnaires were designed to be completed anonymously and mailed to 727 eligible patients. Of those eligible, 232 (32%) returned valid questionnaires. The age at the time reassignment surgery was 44 ± 9 (range 18-70) years and mean duration after surgery was 3 ± 1 (range 1-7) years.

Happiness with sexual function and the reassignment surgery was reported to be lower when permanent vaginal stenosis, clitoral necrosis, pain in the vagina or genitals, or other complications such as infection, bleeding, poor healing, other tissue loss, other tissue necrosis, urinary incontinence, and genital numbness were present. Quality-of-life (QOL) was impaired when pain in the vagina or genitals was present.

Satisfaction with sexual function, gender reassignment surgery, and overall QOL was lower when genital sensation was impaired and when vaginal architecture and lubrication were perceived to be unsatisfactory. Intermittent regret regarding reassignment surgery was associated with vaginal hair and clitoral pain. Vaginal stenosis was associated with surgeries performed longer ago; whereas, more satisfaction with vaginal depth and width was present in more recent surgeries.

f. Prospective, non-blinded, observational, longitudinal and patients served as their own controls

Heylens et al. conducted a prospective, non-blinded observational study using a longitudinal design in which patients served as their own controls. They used a non-specific psychiatric test with normative data along with two self-designed questionnaires. The investigators assessed psychosocial adjustment and psychopathology in patients with gender identity disorders. Patients were to be sequentially evaluated prior to institution of hormonal therapy, then 3 to 6 months after the start of cross-sex hormone treatment, and then again one to 12 months after reassignment surgery. The Dutch version of the SCL-90R with 8 subscales (agoraphobia, anxiety, depression, hostility, interpersonal sensitivity, paranoid ideation/psychoticism, and sleeping problems) and a global score (psycho-neuroticism) was used serially. A seven parameter questionnaire was used serially to assess changes in social function. Another cross-sectional survey assessed emotional state. The cohorts at each time point consisted of patients who were in the treatment cohort at the time and who had submitted survey responses.

Ninety of the patients who applied for reassignment surgery between June 2005 and March 2009 were recruited. Fifty seven entered the study. Forty six (51.1% of the recruited population) underwent reassignment surgery. Baseline questionnaire information was missing for 3 patients. Baseline SCL-90 scores were missing for 1 patient but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. Time point 2 (after hormone therapy) SCL-90 information was missing for 10, but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. At time point 3, 42 (91.3% of those who underwent reassignment surgery) patients completed some part of the SCL-90 survey and the psychosocial questionnaires. Some questionnaires were incomplete. The investigators reported response rates of 73.7% for the psychosocial questionnaires and 82.5% rates the SCL-90.

Of those who responded at follow-up after surgery, 88.1% reported having good friends; 52.4% reported the absence of a relationship; 47.6% had no sexual contacts; 42.9% lived alone; 40.5% were unemployed, retired, students, or otherwise not working; 2.4% reported alcohol abuse; and 9.3% had attempted suicide. The frequency of these parameters reportedly did not change statistically during the study interval, but there was no adjustment for the inclusion of patients who did not undergo surgery.

In a cross-sectional, self-report mood survey, of the 42 study entrants who completed the entire treatment regimen including reassignment surgery and the final assessment (refers to the initial 57) reported improved body-related experience (97.6%), happiness (92.9%), mood (95.2%), and self-confidence (78.6%) and reduced anxiety (81.0%). Of participants, 16.7% reported thoughts of suicide. Patients also reported on the intervention phase that they believed was most helpful: hormone initiation (57.9%), reassignment surgery (31.6%), and diagnostic-psychotherapy phase (10.5%).

The global "psycho-neuroticism" SCL-90R score, along with scores of 7 of the 8 subscales, at baseline were statistically more pathologic than the general population. After hormone therapy, the score for global "psycho-neuroticism" normalized and remained normal after reassignment surgery. More specifically the range for the global score is 90 to 450 with higher scores being more pathologic. The score for the general population was 118.3 ± 32.4 . The respective scores for the various gender dysphoric cohorts were 157.7 ± 49.8 at initial presentation, 119.7 ± 32.1 after hormone therapy, and 127.9 ± 37.2 after surgery. The scores for the general

Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med. 2005 Jan;35(1):89-99.

Smith et al. conducted a prospective, non-blinded, observational study using a longitudinal design and psychological function tools. Patients served as their own control prior to and after reassignment surgery. The investigator assessed gender dysphoria, body dissatisfaction, physical appearance, psychopathology, personality traits, and post-operative function in patients with gender dysphoria. Patients underwent some aspect of reassignment surgery. The test instruments included the Utrecht Gender Dysphoria Scale (12 items), the Body Image Scale adapted for a Dutch population (30 items), Appraisal of Appearance Inventory (3 observers, 14 items), the Dutch Short MMPI (83 items), the Dutch version of the Symptom Checklist (SCL)(90 items), and clinic-developed or modified questionnaires. Pre-treatment data was obtained shortly after the initial interview. Post-surgery data were acquired at least 1 year post reassignment surgery.

The size of the pool of available patients was not identified. Overall 325 consecutive adolescents and adults initially were "involved." Of these, 103 (29 [28.2%] female-to-male patients and 74 [71.8%] male-to-female patients [ratio 1:2.6]) never started hormone therapy; 222 (76 [34.2%] female-to-male patients and 146 [65.8%] male-to-female patients [ratio 1:1.9]) initiated hormone therapy. Of the patients who started hormone therapy, 34 (5 [14.7%] female-to-male patients and 29 [85.3%] male-to-female patients [ratio 1:5.8]) discontinued hormone therapy. After discontinuation of hormone therapy, the study was limited to adults. Of adults, 162 (58 [35.8%] female-to-male and 104 [64.2%] male-to-female [ratio 1:1.8]) were eligible and provided pre-surgical test data, and 126 (77.8% of eligible adults) (49 [38.9%] female-to-male and 77 [61.1%] male-to-female [ratio 1:1.6]) provided post-surgical data. For those patients who completed reassignment, the mean age at the time of surgical request was 30.9 years (range 17.7-68.1) and 35.2 years (range 21.3-71.9) years at the time of follow-up. The intervals between hormone treatment initiation and surgery and surgery and follow-up were 20.4 months (range 12 to 73) and 21.3 months (range 12 to 47) respectively.

Of the 126 adults who provided post-surgical data, 50 (40.0%) reported having a steady sexual partner, three (2.3%) were retired, and 58 (46.0%) were unemployed. Regarding regret, six patients expressed some regret regarding surgery, but did not want to resume their natal gender role, and one male-to-female had significant regret and would not make the same decision.

Post-surgery Utrecht dysphoria scores dropped substantially and approached reportedly normal values. The patients' appearance better matched their new gender. No one was dissatisfied with his/her overall appearance at follow-up. Satisfaction with primary sexual, secondary sexual, and non-sexual body traits improved over time. Male-to-female patients, however, were more dissatisfied with the appearance of primary sex traits than female-to-male patients. Regarding mastectomy, 27 of 38 (71.1%) female-to-male respondents (not including 11 non-respondents) reported incomplete satisfaction with their mastectomy procedure. For five of these patients, the incomplete satisfaction was because of scarring. Regarding vaginoplasty, 20 of 67 (29.8%) male-to-female respondents (not including 10 non-respondents) reported incomplete satisfaction with their vaginoplasty.

Most of the MMPI scales were already in the normal range at the time of initial testing. SCL global scores for psycho-neuroticism were normally elevated pre-surgery 104.1±40.7 (range 90-186) and normalized after surgery 120.3±31.4. (An analysis using patient level data for only the completers was not conducted.)

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. Sexual and Relationship Therapy. 2007 Feb; 22(1):77-81. (Not in PubMed) and Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. Sexual and Relationship Therapy. 2008 May; 23(2):141-5. (Not in PubMed)

Udeze et al. conducted a prospective, non-blinded, longitudinal study assessing a randomized subset of patients who had completed a non-specific psychological function tool prior to and after male-to-female reassignment surgery. Patients served as their own controls. The investigators used the WPATH criteria for patient selection. Psychiatric evaluations were routine. All patients selected for treatment were routinely asked to complete the self-administered SCL-90R voluntarily on admission to the program and post-operatively. A post-operative evaluations (psychiatric and SCL-90R assessment) were conducted within 6 months to minimize previously determined loss rates. The patient pool was domestic and international. There were 546 gender dysphoric patients from all over the United Kingdom and abroad, of whom 318 (58.2%) progressed to surgery. Of these, 127 were from the local Leicester area in the United Kingdom and 38 (29.9%) progressed to surgery. The mean age for the selected male-to-female patients at the time of study was 47.33±13.26 years (range 25 to 80) and reflected an average wait time for surgery of 14 months (range 2 months to 6 years). For this investigation, 40 male-to-female subjects were prospectively selected.

The raw SCL-90 global scores for psycho-neuroticism were unchanged over time: 48.33 prior to surgery and 49.15 after surgery. If the scale was consistent with T-scoring, the results were non-pathologic. A statistical trend in the anger/hostility subscale was reported. No psychiatric disorders were otherwise identified prior to or after surgery.

Investigators from the same clinical group (Megeri, Khoosal, 2007) conducted additional testing to specifically address anxiety and depression with the Beck Depression Inventory, General Health Questionnaire (with 4 subscales), HADS, and Spielberger State and Trait Anxiety Questionnaire (STAI-X1 and STAI-X2). The test population and study design appear to be the same. No absolute data were presented. Only changes in scores were presented. There were no statistically significant changes.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. Arch Sex Behav. 1987 Dec;16(6):511-22.

Kockott and Fahrner conducted a prospective, observational study using a longitudinal design. Treatment cohorts were used as controls, and patients served as their own controls. The investigators assessed psychosocial adjustment in patients with gender identity issues. Patients were to have met DSM III criteria. Transsexuals, 16

The first investigative tool was a semi-structured in-person interview consisting of 125 questions. The second investigative tool was a scale that organized the clinical material into nine domains which were then scored on a scale. The Psychological Integration of Trans-sexuals (PIT) instrument was not otherwise described in the publication or in other citations. There were 15 interviews and two separate interviewers. There were 80 patients identified, but 58 (72.5%) patients (26 pre-operative; 32 post-operative) were ultimately included in the analysis. The duration of follow-up was longer for post-operative patients (6.5 years) than for pre-operative patients (4.6 years) (including time for one patient subsequently excluded). The mean age of the post-operative patients was 35.5 ± 13.1 years, and the age of the patients who maintained a continued desire for surgery was 31.7 ± 10.2 years. The age of the patients who hesitated about surgery was somewhat older, 40.3 ± 9.4 years. The age of the patients who were no longer interested in surgery was 31.8 ± 6.5 years. All were employed or in school at baseline. Patients with hesitation were financially better-off, had longer-standing relationships even if unhappy, and had a statistical tendency to place less value on sex than those with an unchanged wish for surgery.

Post-operative patients more frequently reported contentment with the desired gender and the success of adaption to the gender role than the pre-operative patients with a persistent desire for surgery. Post-operative patients more frequently reported sexual satisfaction than pre-operative patients with a continuing desire for surgery. Post-operative patients also more frequently reported financial sufficiency and employment than pre-operative patients with a persistent desire for surgery. Suicide attempts were stated to be statistically less frequent in the post-surgical cohort.

Psychosocial adjustment scores were in the low end of the range with "distinct difficulties" (19-27) at the initial evaluation for the post-operative patients (19.7), the pre-operative patients with a persistent wish for surgery (20.2), and the hesitant patients (19.7). At initial evaluation, psychosocial adjustment scores for patients no longer wanting surgery were at the high end of the range with "few difficulties" (10-18). At the final evaluation, Psychosocial adjustment scores were at the high end of the range "few difficulties" (10-18) for the post-operative patients (13.2) and the patients no longer wanting surgery (16.5). Psychosocial adjustment scores at the final evaluation were in the borderline range between "few difficulties" (10-18) and "distinct difficulties" (19-27) for both the pre-operative patients with a persistent desire for surgery (18.7), and the hesitant patients (19.1).

The changes in the initial score and the final follow-up score *within* each group were tracked and reported to be statistically significant for the post-operative group, but not for the other groups. Statistical differences *between* groups were not presented. Moreover, the post-operative patients had an additional test immediately prior to surgery. The first baseline score (19.7) would have characterized the patients as having "distinct difficulties" in psychosocial adjustment while the second baseline score (16.7) would have categorized the patients as having "few difficulties" in psychosocial adjustment despite the absence of any intervention except the prospect of having imminent reassignment surgery. No statistics reporting on the change between scores of the initial test and the test immediately prior to surgery and the change between scores of the test immediately prior to surgery and the final follow-up were provided.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry. 1979 Aug;36(9):1010-5. (United States study)

Meyer and Reter conducted a prospective, non-blinded, observational study using a longitudinal design and retrospective baseline data. Interview data were scored with a self-designed tool. There were treatment control cohorts, and patients served as their own controls. The investigators assessed patients with gender dysphoria. The 1971 criteria for surgery required documented cross-sex hormone use as well as living and working in the desired gender for at least 1 year in patients subsequently applying for surgery. Clinical data including initial interviews were used for baseline data. In follow-up, the investigators used extensive 2 to 4 hour interviews to collect information on (a) objective criteria of adaptation, (b) familial relationships and coping with life milestones, and (c) sexual activities and fantasies. The objective criteria, which were the subject of the publication, included employment status (Hollingshead job level), cohabitation patterns, and need for psychiatric intervention. The investigators designed a scoring mechanism for these criteria and used it to determine a global adjustment score.

The clinic opened with 100 patients, but in follow-up, 52 of the 100 patients were interviewed and 50 of the interviewees gave consent for publication. Of these, 15 (4 female-to-male, 11 male-to-female; ratio 1:2.8) were part of the initial operative cohort, 14 (1 female-to-male; 13 male-to-female; ratio 1:13) later underwent reassignment surgery at the institution or elsewhere, and 21 (5 female-to-male; 16 male-to-female; ratio 1:3.2) did not undergo surgery. The mean ages of these cohorts were 30.1, 30.9, and 26.7 years respectively. The mean follow-up time was 62 months (range 19-142) for those who underwent surgery and 25 months (range 15-48) for those who did not. Socioeconomic status was lowest in those who subsequently underwent reassignment surgery.

Of patients initially receiving surgery, 8% had some type of later psychiatric contact, which was approximately 3.5 times higher in those who had not undergone surgery or who had done so later. There was a single female-to-male patient with multiple surgical complications who sought partial reassignment surgery reversal.

The adjustment scores improved over time with borderline statistical significance for the initial operative group and with statistical significance for the never operated group. Both the absolute score value at follow-up and the magnitude of change were the same. By contrast, the adjustment scores did not improve for those who were not in the cohort initially approved for surgery, but who subsequently underwent surgery later. This was particularly true if the surgery was performed elsewhere.

h. Prospective, non-blinded, observational, semi-cross sectional with no controls

Johansson et al. conducted non-blinded, observational study using a semi-cross-sectional design (albeit over an extended time interval) using a self-designed tool and Axis V assessment. The study was prospective except for the acquisition of baseline Axis V data. There were no formal controls in this mixed population with and without surgery.

The investigators assessed satisfaction with the reassignment process, employment, partnership, sexual function, mental health, and global satisfaction in gender-reassigned persons from two disparate geographic regions. No other information regarding the sites of care was provided. Surgical candidates were required to have met National Board of Health and Welfare criteria including initial and periodic psychiatric assessment, ≥ 1 year of real-life experience in preferred gender, and ≥ 1 year of subsequent hormone treatment. In addition, participants were required to have been approved for reassignment 5 or more years prior and/or to have completed surgical reassignment (e.g., sterilization, genital surgery) 2 or more years prior. The investigators employed semi-structured interviews covering a self-designed list of 55 pre-formulated questions with a 3 or 5 point ordinal scale. Clinician assessment of Global Assessment of Functioning (GAF; Axis V) was also conducted and compared to initial finding during the study. Changes or differences considered to be biologically significant were not pre-specified. Diagnostic cut points were not provided. Statistical corrections for multiple comparisons were not included. There was no stratification by treatment.

Of the pool of 60 eligible patients, there were 21 (35.0%) female-to-male and 39 (65%) male-to-female (ratio 1:1.9) ; 32 (53.3% of eligible) (14 [43.8%] female-to-male; 18 [56.2%] male-to-female [ratio 1:1.3]) had completed genital gender reassignment surgery (not including 1 post mastectomy), 5 were still in the process of completing surgery, and 5 (1 female-to-male; 4 male-to-female; ratio 1:4) had discontinued the surgical process prior to castration and genital surgery.

The ages of the patients (ranges) at entry into the program, reassignment surgery, and follow-up were 27.8 (18-46), 31.4 (22-49), and 38.9 (28-53) in the female-to-male group respectively and 37.3 (21-60), 38.2 (22-57), and 46.0 (25.0-69.0) in the male-to-female group respectively. The differences in age by cohort group were statistically significant. Of participants, 88.2% of all enrolled female-to-male versus 44.0% of all enrolled female-to-male patients had cross-gender identification in childhood (versus during or after puberty) ($p < 0.01$).

Although 95.2% of all enrolled patients self-reported improvement in GAF, in contrast, clinicians determined GAF improvement in 61.9% of patients. Clinicians observed improvement in 47% of female-to-male patients and 72% of male-to-female patients. A ≥ 5 point improvement in the GAF score was present in 18 (42.9%). Of note, three of the five patients who were in the process of reassignment and five of the five who had discontinued the process were rated by clinicians as having improved.

patients, 33 (79%) identified themselves by their preferred gender and nine (21%) identified themselves as transgender. Case 7:16-cv-00108-Q Document 26 Filed 10/21/16 Page 624 of 919 PageID 1090
Of these nine (eight female-to-male and one who completed reassignment surgery because of ambivalence secondary to lack of acceptance by others and dissatisfaction with their appearance. Of the patients who underwent genital surgery (n=32) and mastectomy only (n=1), 22 (66.7%) were satisfied while four (three female-to-male) were dissatisfied with the surgical treatment.

Regarding relationships after surgery, 16 (38%) (41% of female- to-male; 36% of male-to-female) were reported to have a partner. Yet more than that number commented on partner relationships: 62.2 % of the 37 who answered (50.0% of female- to-male; 69.6% of male-to-female) reported improved partner relationships (5 [11.9%] declined to answer.); 70.0% of the 40 who answered (75.0% of female-to-male; 66.7% of male-to-female) reported an improved sex life. Investigators observed that reported post-operative satisfaction with sex life was statistically more likely in those with early rather than late cross-gender identification.

In addition 55.4% self-reported improved general health; 16.1% reported impaired general health; 11.9% were currently being treated with anti-depressants or tranquilizers; 44.7 % of the 38 who answered (53.3% of female-to-male; 39.1% of male-to-female) reported improved work circumstances (4 [9.5%] declined to answer.); 61.9% were students or employed. The remainder (38.1%) were living on disability pensions (28.6%), unemployed (4.8%), or retired (4.8%).

i. Prospective, cross sectional, observational, internet self- report survey, with unknown blinding, no formal controls

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. Qual Life Res. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. (United States study)

Newfield et al. conducted a prospective, observational internet self-report survey of unknown blinding status using a cross-sectional design and a non-specific quality of life tool in a mixed, population with and without reassignment surgery. There were no formal controls.

The investigators recruited natal female participants identifying as male using email, internet bulletin boards, and flyers/postcards distributed in the San Francisco Bay Area. Reduction of duplicate entries by the same participant was limited to the use of a unique user name and password.

The investigators employed the SF-36 Version 2 using U.S. normative data. They reported using both male and female normative data for the comparator SF-36 cohort. Data for the 8 domains were expressed as normative scoring. The Bonferroni correction was used to adjust for the risk of a Type 1 error with analyses using multiple
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A total of 379 U.S. respondents classified themselves as males or females to males with or without therapeutic intervention. The mean age of the respondents who classified themselves as male or female-to-male was 32.6 ± 10.8 years. 89% were Caucasian, 3.6% Latino, 1.8% African American, 1.8% Asian, and 3.8% other. 254 (67.0%) reported any testosterone use in the past or currently; and 242 (63.8%) reported current testosterone use. In addition, 136 (36.7%) reported having had "top" surgery and 11 (2.9%) reported having "bottom" surgery. The Physical Summary Score (53.45 ± 9.42) was statistically higher (better) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was within 1 standard deviation of the normative mean. The Mental Summary Score (39.63 ± 12.2) was statistically lower (worse) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was well within 2 standard deviations of the normative mean. Subcomponents of this score: Mental Health (42.12 ± 10.2), Role Emotional (42.42 ± 11.6), Social Functioning (43.14 ± 10.9), and Vitality (46.22 ± 9.9) were statistically lower (worse) than the SF-36 normative sub-scores, but well within 1 standard deviation of the normative sub-score means. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

Additional intragroup analyses were conducted, although the data were not stratified by type of therapeutic intervention (hormonal, as well as, surgical). Outcomes of hormone therapy were considered separately and dichotomously from reassignment surgery. The Mental Summary Score was statistically higher (better) in those who had "Ever Received Testosterone" (41.22 ± 11.9) than those with "No Testosterone Usage" (36.08 ± 12.6) ($p = 0.001$). The Mental Summary Scores showed a trend towards statistical difference between those who "Ever Received Top Surgery" (41.21 ± 11.6) and those without "Top Surgery" (38.01 ± 12.5) ($p = 0.067$). These differences were well within 1 standard deviation of the normative mean. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

j. Partially prospective, non-blinded, observational studies with longitudinal designs and patients served as their own controls

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. Arch Sex Behav. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18.

Ruppin and Pfäfflin conducted a partially prospective, non-blinded, observational study using a longitudinal design and non-specific psychometric tests and a self-designed interview tool and questionnaire. Patients served as their own controls.

The investigators assessed psychological symptoms, interpersonal difficulties, gender role stereotypes, personality characteristics, societal function, sexual function, and satisfaction with new gender role in patients with gender dysphoria. Patients were required to have met the ICD-10 criteria for trans-sexualism, been seen by the clinic by prior to 2001, and completed an official change in gender including name change prior to 2001. Assessment tools included German versions of standardized surveys with normative data: the SCL 90-R, the

Overall, 140 patients received recruitment letters then 71 (50.7%) agreed to participate. Of these participants, 36 (50.7%) were female-to-male; 35 (49.3%) were male-to-female (ratio 1:0.97). The ages of the patients were: 41.2 ± 5.78 years female-to-male and 52.9 ± 10.82 years male-to-female 52.9 ± 10.82 years. The intervals for follow-up were 14.1 ± 1.97 years and 13.7 ± 2.17 years respectively.

All female-to-male patients had undergone mastectomy; 91.7% had undergone oophorectomy and/or hysterectomy; 61.1% had undergone radial forearm flap phalloplasty or metaoidioplasty; 94.3% of male-to-female patients had undergone vaginoplasty and perhaps an additional procedure (breast amplification, larynx surgery, or vocal cord surgery). Two male-to-female patients had not undergone any reassignment surgery, but were still included in the analyses.

A total of 68 patients ranked their well-being as 4.35 ± 0.86 out of five (three patients did not respond to this question). Of respondents, 40% reported not in a steady relationship. Regular sexual relationships were reported by 57.1% of 35/36 female-to-male respondents and 39.4% of 33/35 of male-to-female respondents (three patients did not respond to this question). A total of 11 patients reported receiving out-patient psychotherapy; 69 did not express a desire for gender role reversal (two did not respond to this question). The response rate was less than 100% for most of the self-designed survey questions.

Changes from the initial visit to the follow-up visit were assessed for the SCL-90R in 62 of 71 patients. Changes from the initial visit to the follow-up visit were assessed for the IIP in 55 of 71 patients. Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 58 of 71 patients. The effect size was large only for the "Life Satisfaction" scale. Changes from the initial visit to the follow-up visit were assessed for the BSRI in 16 of 36 female-to-male patients and 19 of 35 male-to-female patients. The "Social Desirability" score increased for the female-to-male respondents. At endpoint, both categories of respondents reported androgynous self-images.

k. Partially prospective, non-blinded, observational studies with cross-sectional designs that had control groups but were not concurrent

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatr Scand.* 2000 Oct;102(4):276-81.

In the germane sub-study, the investigator assessed psychopathology in patients with gender dysphoria. Patients, who were independently evaluated by 2 senior psychiatrists, were required to meet DSM III-R or DSM IV diagnostic criteria and the Swedish criteria for reassignment surgery. The Norwegian version of the SCL-90 was used. The testing was conducted from 1987 to 1989 for those who had undergone reassignment surgery between 1963 and 1987 and from 1996 to 1998 for pre-surgical patients who had applied for reassignment surgery between 1996 and 1998. In addition, Axis I, Axis II, and Axis V (Global Functioning) was assessed.

Of 65 post-surgical and 34 pre-surgical patients, 59 post-surgical and 27 pre-surgical patients ultimately entered the study. The combined cohorts consisted of 35 (40.7%) female-to-male patients and 51 (59.3%) male-to-female patients (ratio 1:1.5). The ages were female-to-male 34 ± 9.5 years and female-to-male 33.3 ± 10.0 years. The other control group consisted of patients with personality disorder. 101 (27 men (33.9 ± 7.3 years) and 74 women (31.6 ± 8.2)) were tested during a treatment program. One year later, 98% were evaluated.

A total of 28 (32.5%) of the pre- and post- reassignment surgery patients had an Axis I diagnosis compared to 100 (99.0%) of those with personality disorders. Depression and anxiety were the most common diagnoses in both groups, but were approximately three to four times more common in the personality disorder cohort. Seventeen (19.8%) of the pre- and post- reassignment surgery patients had an Axis II diagnosis whereas the mean number of personality disorders in the personality disorder cohort was 1.7 ± 1 . The Global Assessment of Function was higher (better) in the gender dysphoric groups 78.0 ± 8.9 than in the personality disorder cohort (53.0 ± 9.0).

Global Severity Indices (GSI) were highest for those with personality disorder regardless of gender and exceeded the cut-point score of 1.0. The GSI scores for females-to-males and males-to-females were 0.67 ± 0.57 and 0.56 ± 0.45 . Although they were nominally higher than the healthy normative controls (males: 0.32 ± 0.36 and females 0.41 ± 0.43), they were well within the non-pathologic range. The same was true for the subscales.

SCL-90 GSI scores did not differ substantively between pre- and post-surgical patients, nor did the SCI subscale scores differ substantively between pre- and post-surgical patients. Any small non-significant differences tracked with the age and sex differences.

I. Partially prospective, non-blinded, observational studies with cross-sectional designs that had no control groups

Leinung et al. conducted a partially prospective, non-blinded, observational study using a cross-sectional design and descriptive statistics. There were no formal controls. The investigators assessed employment, substance abuse, psychiatric disease, mood disorders, Human Immunodeficiency Virus (HIV) status in patients who had met WPATH guidelines for therapy, and who had initiated cross-sex hormone treatment.

A total of 242 patients treated for gender identity disorder in the clinic from 1992 through 2009 inclusive were identified. The number of those presenting for therapy almost tripled over time. Of these patients, 50 (20.7%) were female-to-male; 192 (79.3%) male-to-female (ratio 1:3.8).

The age of female-to-male and male-to-female patients with gender dysphoria at the time of clinic presentation was 29.0 and 38.0 years respectively.

The female-to-male and male-to-female patients with gender dysphoria at the time of hormone initiation were young: 27.5 and 35.5 years old respectively ($p < 0.5$). Of the male-to-female cohort, 19 (7.8%) had received hormone therapy in the absence of physician supervision; 91 (37.6%) had undergone gender-reassignment surgery (32 female-to-male [64.0% of all female-to-male; 35.2% of all surgical patients]; 59 male-to-female [30.7% of all male-to-female; 64.8% of all surgical patients]; ratio 1:1.8).

Psychiatric disease was more common in those who initiated hormone therapy at an older age (> 32 years) 63.9% versus 48.9% at a younger age and by natal gender (48.0% of female-to-male; 58.3% male-to-female). Mood disorders were more common in those who initiated hormone therapy at an older age (> 32 years) 52.1% versus 36.0% at a younger age and this finding did not differ by natal gender (40.0% of female-to-male; 44.8% male-to-female). The presence of mood disorders increased the time to reassignment surgery in male-to-female patients. Of participants 36.4% were employed in jobs requiring a high school degree or less; 28.1% (excluding students) were on disability and/or unemployed. Rates of disability and unemployment were higher in male-to-female patients (31.8%) than female-to-male patients (14.0%). Mental health diagnoses reportedly were the major reason for disability. HIV infection and substance abuse were higher in male-to-female patients than female-to-male patients (8.3% versus 0% and 12.5% versus 6.0% respectively).

m. Retrospective, non-blinded, observational, longitudinal studies

Asscheman et al. conducted a retrospective, non-blinded, observational study of mortality using a longitudinal design of population treated with hormones, as well as, reassignment surgery and a population-based cohort. The investigators assessed mortality in patients who (a) were from a single-center, unspecified, university specialty clinic, (b) initiated cross-sex hormone treatment prior to July 1, 1997, and (c) had been followed by the clinic for at least 1 year or had expired during the first year of treatment. The National Civil Record Registry (Gemeentelijke Basis Administratie) was used to identify/confirm deaths of clinic patients. Information on the types or hormones used was extracted from clinic records, and information on the causation of death was extracted from medical records or obtained from family physicians. Mortality data for the general population was obtained through by the Central Bureau of Statistics of the Netherlands. Mortality data from Acquired Immune Deficiency Syndrome (AIDS) and substance abuse were extracted from selected Statistics Netherlands reports. The gender of the general Dutch population comparator group was the natal sex of the respective gender dysphoric patient groups.

A total of 1,331 patients who met the hormone treatment requirements were identified (365 female-to-male [27.4%]; 966 male-to-female [72.6%]; ratio 1:2.6). Of these, 1,177 (88.4%) underwent reassignment surgery (343 [94.0% of female-to-male entrants]; 834 [86.3% of male-to-female entrants]; ratio 1:2.4; $p < 0.0001$). The mean age at the time of hormone initiation in female-to-male and male-to-female patients was young: 26.1 ± 7.6 (range 16–56) years and 31.4 ± 11.4 (range 16–76) years respectively, although the male-to-female subjects were relatively older ($p < 0.001$). The mean duration of hormone therapy in female-to-male and male-to-female patients was 18.8 ± 6.3 and 19.4 ± 7.7 years respectively.

There were a total of 134 deaths in the clinic population using hormone therapy as well as reassignment surgery. Of the patients, 12 (3.3%) of the 365 female-to-male patients and 122 (12.6%) of the 966 male-to-female patients died. All-cause mortality was 51% higher and statistically significant (Standardized Mortality Ratio [SMR] 95% confidence interval [CI] 1.47–1.55) for males-to-females when compared to females in the general Dutch population. The small increase in all-cause mortality (12%) for females-to-males when compared to males in the general Dutch population was not statistically significant; 95% CI 0.87–1.42.

The major known contributors to the mortality difference between male-to-female patients and the Dutch population at large were completed suicide ($n=17$, SMR 5.70 [95% CI 4.93–6.54]), AIDS ($n=16$, SMR 30.20 [95% CI 26.0–34.7]), and illicit drug use ($n=5$, SMR 13.20 [95% CI 9.70–17.6]). An additional major contributor was “unknown cause” ($n=21$, SMR 4.00 [95% CI 3.52–4.51]). Of the 17 male-to-female hormone treated patients who committed suicide, 13 (76.5%) had received prior psychiatric treatment and 6 (35.3%) had not undergone reassignment surgery because of concerns about mental health stability.

Ischemic heart disease was a major disparate contributor to excess mortality in male-to-female patients in older patients ($n=18$, SMR 1.64 [95% CI 1.43–1.87], mean age [range]: 59.7 [42–79] years. Current use of a particular type of estrogen, ethinyl estradiol, was found to contribute to death from myocardial infarction or stroke (Adjusted Hazard Ratio 3.12 [95% CI 1.28–7.63], $p=0.01$). There was a smaller, but statistically significant increase in lung cancer that was thought to possibly be related to higher rates of smoking in this cohort.

Although overall mortality was not increased in the hormone-treated female-to-male patients, there were more deaths due to illicit drug use than expected (SMR 25 [6.00-32.5]).

n. Retrospective, non-blinded, observational, longitudinal studies using matched national data

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One. 2011;6(2):e16885. Epub 2011 Feb 22.

Dhejne et al. conducted a retrospective, non-blinded, observational study of nation-wide mortality using a longitudinal and a population-based matched cohort. The investigators assessed mortality, suicide attempts, psychiatric hospitalization, and substance abuse in gender-reassigned persons and randomly selected unexposed controls matched by birth year and natal sex (1:10) as well as by birth year and the reassigned gender (1:10). Data were extracted from national databases including the Total Population Register (Statistics Sweden), the Medical Birth Register, the Cause of Death Register (Statistics Sweden), the Hospital Discharge Register (National Board of Health and Welfare), the Crime Register (National Council of Crime), and those from the Register of Education for highest educational level. The criteria required to obtain the initial certificate for reassignment surgery and change in legal status from the National Board of Health and Welfare were not delineated, but included evaluation and treatment by one of 6 specialized teams, name change, a new national identity number, continued use of hormones, and sterilization/castration. Descriptive statistics with hazard ratios were provided. There were 804 patients identified with gender identity disorder (or related disorder) in Sweden during the period from 1973 to 2003 inclusive. Of these patients, 324 (40.3%) underwent gender-reassignment surgery (133 female-to-male [41.0%]; 191 male-to-female [59.0%]; ratio 1:1.4). The average follow-up time for all-cause mortality was 11.4 years (median 9.1). The average follow-up time for psychiatric hospitalization was 10.4 years (median 8.1).

The mean ages in female-to-male and male-to-female reassigned patients were: 33.3 ± 8.7 (range 20–62) and 36.3 ± 10.1 (range 21–69) respectively. Immigrant status was two times higher in reassigned patients ($n=70$, 21.6%) than in either type of control (birth [natal] sex matched $n=294$ [9.1%] or reassigned gender matched $n=264$ [8.1%]). Educational attainment (10 or more years) was somewhat lower for reassigned patients ($n=151$ [57.8%]) than in either type of control (birth sex matched $n=1,725$ [61.5%] or reassigned gender matched $n=1804$ [64.3%]) (cohort data were incomplete). The biggest discordance in educational attainment was for female-to-male reassigned patients regardless of the control used. Prior psychiatric morbidity (which did not include hospitalization for gender dysphoria) was more than four times higher in reassigned patients ($n=58$, 17.9%) than in either type of control (birth sex matched $n=123$ [3.8%] or reassigned gender matched $n=114$ [3.5%]).

All-cause mortality was higher for patients who underwent gender reassignment surgery ($n=27$ [8.3%]) than in controls (hazard ratio 2.8 [1.8-4.3]) even after adjustment for covariants (prior psychiatric morbidity and immigration status). Divergence in the survival curves began at 10 years. The major contributor to this mortality difference was completed suicide ($n=10$ [3.1%]; adjusted hazard ratio 19.1 [5.8-62.9]). Mortality due to cardiovascular disease was modestly higher for reassigned patients ($n=9$ [2.8%]) than in controls (hazard ratio 2.5 [1.2-5.3]).

Suicide attempts were more common in patients who underwent gender reassignment surgery ($n = 29$ [9.0%] than in controls (adjusted hazard ratio 4.9 [2.9–8.5]). Male- to-female patients were at higher adjusted risk for attempted suicide than either control whereas female-to-male patients were at higher adjusted risk compared to only male controls and maintained the female pattern of higher attempted suicide risk. Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common in reassigned persons $n = 64$ [20.0%] than in controls (hazard ratio 2.8 [2.0–3.9]) even after adjusting for prior psychiatric morbidity. Hospitalization for substance abuse was not greater than either type of control. The increased risk for conviction of any crime or violent crime observed during the 1973-1988 interval was not seen later.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. Arch Sex Behav. 2014 Nov;43(8):1535-45. Epub 2014 May 29 and Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand. 1998 Apr;97(4):284 (Dhejne et al., 2014; Landen et al., 1998) Sweden-All

Dhejne et al. conducted a non-blinded, observational study that was longitudinal for the capture of patients with “regret” in a national database. This same group (Landen et al., 1998) conducted a similar study along with retrospective acquisition of clinical data to explore the differences between the cohorts with and without regret. There were no external controls; only intra-group comparisons for this surgical series.

The investigators assessed the frequency of regret for gender reassignment surgery. Data were extracted from registries at the National Board of Health and Welfare to which patients seeking reassignment surgery or reversal of reassignment surgery make a formal application and which has maintained such records since a 1972 law regulating surgical and legal sex reassignment. The investigators reviewed application files from 1960 through 2010. The specific criteria to qualify for gender surgery were not delineated. Patients typically underwent diagnostic evaluation for at least 1 year. Diagnostic evaluation was typically followed by the initiation of gender confirmation treatment including hormonal therapy and real-life experience. After 2 years of evaluation and treatment, patients could make applications to the national board. Until recently sterilization or castration were the required minimal surgical procedures. (Dhejne et al., 2011) Secular changes in this program included consolidation of care to limited sites, changes in accepted diagnostic criteria, and provision of non-genital surgery, e.g., mastectomy during the real-life experience phase, and family support.

Of the 767 applicants for legal and surgical reassignment (289 [37.7%] female-to-male and 478 [62.3%] male-to-female; ratio 1:1.6]. The number of applicants doubled each ten year interval starting in 1981.

Of the applicants, 88.7% or 681 (252 [37.0%] female-to-male and 429 [63.0%] male-to-female; ratio 1:1.7] had undergone surgery and changed legal status by June 30, 2011. This number included eight (four [50.0%] female to-male and four [50.0%] male to female; ratio 1:1) people who underwent surgery prior to the 1972 law. (This number [6.0%] appears to include 41 (two [4.9%] female-to-male and 39 [95.1%] male-to-female; ratio 1:19.5) people who underwent surgery abroad at their own expense [usually in Thailand or the U.S.]. This cohort includes one person who was denied reassignment surgery by Sweden.)

Twenty-five (3.3%) of the applications were denied with the two most common reasons being an incomplete application or not meeting diagnostic criteria. An additional 61(8.0%) withdrew their application, were wait-listed for surgery, postponed surgery (perhaps in hopes of the later revocation of the sterilization requirement), or were granted partial treatment.

The formal application for reversal of the legal gender status, the "regret rate", was 2.2%. No one who underwent sex-reassignment surgery outside of Sweden (36 of 41 after 1991) has requested reversal. The authors noted, however, that this preliminary number may be low because the median time interval to reversal request was eight years-only three of which had elapsed by publication submission- and because it was the largest serial cohort. This number did not include other possible expressions of regret including suicide (Dhejne et al., 2011).

Dhejne et al. in 2014 reported that the female-to-male: male-to-female ratio among those who made formal applications for reversal was 1:2. The investigators also reported that the female-to-male applicants for reversal were younger than the entire female-to-male cohort (median age 22 versus 27 years) while the male-to-female applicants for reversal were older than the entire male-to-female cohort (median age 35 versus 32 years). Other clinical data to explore the differences between the cohorts with and without regret were not presented in this update publication.

In their earlier publication, in addition to determining a regret rate (3.8%), Landen et al. extracted data from medical records and government verdicts. Logistic regression analyses were used identify relationships between variables. They observed that: (a) 25.0% of the cohort with regrets and 11.4% of the cohort without regrets were unemployed, (b) 16.7% of the cohort with regrets and 15.4% of the cohort without regrets were on "sick benefit", (c) 15.4% of the cohort with regrets and 13.9% of the cohort without regrets had problems with substance abuse, (d) 69.2% of the cohort with regrets and 34.6% of the cohort without regrets had undergone psychiatric treatment, (e) 15.4% of the cohort with regrets and 8.8% of the cohort without regrets had a mood disorder, and (f) 15.4% of the cohort with regrets and 1.5% of the cohort without regrets had a psychotic disorder.

The putative prognostic factors that were statistically different (albeit without Bonferroni correction) between the cohorts with and without regret included prior psychiatric treatment, a history of psychotic disorder, atypical features of gender identity, and poor family support. Factors that trended towards statistical difference included having an unstable personality, sexual orientation and transvestitism. These variables were tested with logistic regression. Initial modeling included the variable "history of psychotic disorder". Although this variable was predictive, it was excluded from future analyses because it was already a contraindication to reassignment surgery. Additional analyses identified poor family support as the most predictive variable and atypical features of gender identity as the second most important variable. Presence of both variables has a more than additive effect.

The nationwide mortality studies by Dhejne et al. 2011 includes much, if not all, of the Landen (1998) patient population and most of the Dhejne (2014) population.

o. Randomized, non-blinded, longitudinal, some patients served as their own controls

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry. 1990 Aug;157:261-4.

Mate-Kole et al. conducted a prospective, non-blinded, controlled, randomized, longitudinal study using investigator-designed patient self-report questionnaires and non-specific psychological tests with some normative data. The investigators assessed neuroticism and sex role in natal males with gender dysphoria who had qualified for male-to-female reassignment surgery at a single-center specialty clinic. Forty sequential patients were alternately assigned to early reassignment surgery or to standard wait times for reassignment surgery. Patients were evaluated after acceptance and 2 years later. The criteria used to qualify for gender surgery were the 1985 standards from the Harry Benjamin International Gender Dysphoria Association. These included a ≥ 2 year desire to change gender, a ≥ 1 year demonstrable ability to live and be self-supporting in the chosen gender, and psychiatric assessment for diagnosis and reassessment at 6 months for diagnostic confirmation and exclusion of psychosis. Reassignment surgery was defined as orchidectomy, penectomy, and construction of a neo-vagina. The instruments used were the CCEI for psychoneurotic symptoms and the Bem Sex Role Inventory along with an incompletely described investigator-designed survey with questions about social life and sexual activity. The mean age and range of the entire cohort was 32.5 years (21-53).

Members of the early surgery cohort had a history of attempted suicide (one patient), psychiatric treatment for non-gender issues (six patients), and first degree relatives with psychiatric histories (four patients). Members of the standard surgery cohort were similar, with a history of attempted suicide (two patients), psychiatric treatment for non-gender issues (five patients), and first degree relatives with psychiatric histories (six patients). The early surgery group had surgery approximately 1.75 years prior to the follow-up evaluation. In both groups, cross-dressing began at about age 6.

At baseline, the Bem Sex Role Inventory femininity scores were slightly higher than masculinity scores for both cohorts and were similar to Bem North American female normative scores. The scores did not change in either group over time.

At baseline, the scores for the CCEI individual domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were similar for the cohorts. The total CCEI scores for the two cohorts were consistent with moderate symptoms. Over the 2 year interval, total CCEI scores increased for standard wait group and approached the relatively severe symptom category. During the same interval, scores dropped into the asymptomatic range for the post-operative patients.

The investigator-designed survey assessed changes in social and sexual activity of the prior 2 years, but the authors only compared patients in a given cohort to themselves. Though the researchers did not compare

statistical studies to compare the differences between the 2 cohorts, they did report increased participation in some, but not all, types of recreational activities such as sports (30/20 group), gardening, fishing, going to the pub, and visiting others. Sexual interest also increased. By contrast, pre-operative patients did not increase their participation in these activities. Work status remained the same for post-operative patients which unemployment increased in the standard wait pre-operative cohort.

2. External Technology Assessments

- a. CMS did not request an external technology assessment (TA) on this issue.
- b. There were no AHRQ reviews on this topic.
- c. There are no Blue Cross/Blue Shield Health Technology Assessments written on this topic within the last three years.
- d. There were two publications in the COCHRANE database, and both were tangentially related.

Both noted that there are gaps in the clinical evidence base for gender reassignment surgery.

Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations
Boehmer U. *Am J Public Health*. 2002; 92: 1125-30.

"Findings supported that LGBT issues have been neglected by public health research and that research unrelated to sexually transmitted diseases is lacking."

"Further research is needed but must use more sophisticated designs with comparison groups. This systematic review demonstrated that there are so many gaps in knowledge around LGBT health that a wide variety of studies are needed."

e. There were no National Institute for Health and Care Excellence (NICE) reviews/guidance documents on this topic.

f. There was a technology assessment commissioned by the New Zealand Ministry of Health and conducted by New Zealand Health Technology Assessment (NZHTA) (Christchurch School of Medicine and the University of Otago).

Tech Brief Series: Transgender Re-assignment Surgery Day P. *NZHTA Report*. February 2002;1(1).
http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf

The research questions included the following: (1) Are there particular subgroups of people with transsexualism who have met eligibility criteria for gender reassignment surgery (GRS) where evidence of effectiveness of that surgery exists? And (2) If there is evidence of effectiveness, what subgroups would benefit from GRS?" Based upon the research, "Some 593 possibly relevant articles in abstract form were identified of which 70 articles were retrieved in full text."

The NZHTA stated, "The reviewed studies may indicate that early, rather than delayed, sex reassignment surgery is of greater benefit to transsexual people who have gone through rigorous assessment procedures and have been accepted for surgery. Also, the reviewed studies identify characteristics of groups defined as core and non-core transsexual people, but these characteristics are heterogeneous and anecdotal."

The NZHTA also stated, "Gender reassignment surgery may benefit some carefully assessed and selected transsexual people who have satisfied recognized diagnostic and eligibility criteria, and have received recognized standards of care for surgery. More research is required to improve the evidence base identifying the subgroups of transsexual people most likely to benefit from sex reassignment surgery."

CMS did not convene a MEDCAC meeting.

4. Evidence-Based Guidelines

a. American College of Obstetricians and Gynecologists (ACOG)

Though ACOG did not have any evidence-based guidelines on this topic, they did have the following document:

Health Care for Transgender Individuals: Committee Opinion

Committee on Health Care for Underserved Women; The American College of Obstetricians and Gynecologists. Dec 2011, No. 512. Obstet Gynecol. 2011;118:1454-8.

“Questions [on patient visit records]

should be framed in ways that do not make assumptions about gender identity, sexual orientation, or behavior. It is more appropriate for clinicians to ask their patients which terms they prefer. Language should be inclusive, allowing the patient to decide when and what to disclose. The adoption and posting of a nondiscrimination policy can also signal health care providers and patients alike that all persons will be treated with dignity and respect. Assurance of confidentiality can allow for a more open discussion, and confidentiality must be ensured if a patient is being referred to a different health care provider. Training staff to increase their knowledge and sensitivity toward transgender patients will also help facilitate a positive experience for the patient.”

b. American Psychiatric Association

The American Psychiatric Association (APA) was unable to identify any Randomized Controlled Trials (RCTs) regarding mental health issues for transgender individuals.

"There are some level B studies examining satisfaction/regret following sex reassignment (longitudinal follow-up after an intervention, without a control group); however, many of these studies obtained data retrospectively and without a control group (APA level G). Overall, the evidence suggests that sex reassignment is associated with an improved sense of well-being in the majority of cases, and also indicates correlates of satisfaction and regret. No studies have directly compared various levels of mental health screening prior to hormonal and surgical treatments on outcome variables; however, existing studies suggest that comprehensive mental health screening may be successful in identifying those individuals most likely to experience regrets."

Relevant Descriptions of APA Evidence Coding System/Levels:

[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial."

[G] Other. Opinion-like essays, case reports, and other reports not categorized above."

c. Endocrine Society

Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. *J Clin Endocrinol Metab*. 2009;94:3132-54.

This guideline primarily addressed hormone management and surveillance for complications of that management. A small section addressed surgery and found the quality of evidence to be low.

"This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low."

d. World Professional Association for Transgender Health (WPATH)

Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (Version 7). Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R, Wylie KR, Zucker K. www.wpath.org/files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf *Int J Transgend.* 2011;13:165–232.

The WPATH is "an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health."

WPATH reported, "The standards of care are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b)."

The WPATH standards of care (SOC) "acknowledge the role of making informed choices and the value of harm-reduction approaches."

The SOC noted, "For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one's gender identity);
- Hormone therapy to feminize or masculinize the body;
- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience."

The SOC were carefully reviewed because they are frequently cited as the basis of management by clinicians, including some of the clinical groups with whom CMS spoke used it as a flexible guide. In the WPATH's SOC Appendix D titled "Evidence for Clinical Outcomes of Therapeutic Approaches," WPATH noted, "One of the real supports for any new therapy is an outcome analysis. Because of the controversial nature of sex reassignment surgery, this type of analysis has been very important. Almost all of the outcome studies in this area have been retrospective." They further reported, "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria."

e. American Psychological Association

Suggested citation until formally published in the *American Psychologist*: American Psychological Association. (2015):

Guidelines for Psychological Practice with Transgender and Gender Nonconforming People

Adopted by the Council of Representatives, August 5 & 7, 2015.

www.apa.org/practice/guidelines/transgender.pdf

"The purpose of the Guidelines for Psychological Practice with Transgender and Gender Nonconforming People (hereafter Guidelines) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and transaffirmative psychological practice with TGNC people."

"These Guidelines refer to psychological practice (e.g., clinical work, consultation, education, research, training) rather than treatment."

5. Other Reviews

The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. (Study Sponsor: The National Institutes of Health). Issued March 31, 2011. <http://www.nationalacademies.org/hmd/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and-Transgender-People.aspx>

"To advance understanding of the health needs of all LGBT individuals, researchers need more data about the demographics of these populations, improved methods for collecting and analyzing data, and an increased participation of sexual and gender minorities in research. Building a more solid evidence base for LGBT health concerns will not only benefit LGBT individuals, but also add to the repository of health information we have that pertains to all people."

"Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

b. National Institutes of Health (NIH)

National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf

In response to the IOM report, the NIH LGBT research Coordinating Committee noted that most of the health research for this set of populations is "focused in the areas of Behavioral and Social Sciences, HIV (human immunodeficiency virus)/AIDS, Mental Health, and Substance Abuse. Relatively little research has been done in several key health areas for LGBT populations including the impact of smoking on health, depression, suicide, cancer, aging, obesity, and alcoholism."

6. Pending Clinical Trials

NCT01072825 (Ghent, Belgium sponsor) European Network for the Investigation of Gender Incongruence (ENIGI) is assessing the physical and psychological effects of the hormonal treatment of transgender subjects in two years prior to reassignment surgery and subsequent to surgery. This observational cohort study started in 2010 and is still in progress.

7. Consultation with Outside Experts

Consistent with the authority at 1862(I)(4) of the Act, CMS consulted with outside experts on the topic of treatment for gender dysphoria and gender reassignment surgery.

Given that the majority of the clinical research was conducted outside of the United States, and some studies took place in a or suggested continuity-of-care and coordination-of-care were beneficial to health outcomes, we conducted expert interviews with centers across the U.S. that provided some form of specialty-focused or coordinated care for transgender patients. These interviews informed our knowledge about the current healthcare options for transgender people, the qualifications of the professionals involved, and the uniqueness of treatment options. We are very grateful to the organizations that made time to discuss treatment for gender dysphoria with us.

From our discussions with the all of the experts we spoke with, we noted the following practices in some centers: (1) specialized training for all staff about transgender healthcare and transgender cultural issues; (2) use of an intake assessment by either a social worker or health care provider that addressed physical health, mental health, and other life factors such as housing, relationship, and employment status; (3) offering primary care services for transgender people in addition to services related to gender-affirming therapy/treatments; (4) navigators who connected patients with name-change information or other legal needs related to gender; (5) counseling for individuals, groups, and families; (6) an informed-consent model whereby individuals were often referred to as “clients” instead of “patients,” and (7) an awareness of depression among transgender people (often measured with tools such as the Adult Outcomes Questionnaire and the Patient Health Questionnaire (8) and how, in some instances, with hormone treatment for gender dysphoria, the depression lessens.

8. Public Comments

During the initial comment period, we received 103 comments. Of those, 78% supported coverage of gender reassignment surgery, 15% opposed, and 7% were neutral. The majority of comments supporting coverage were from individuals and advocacy groups. All of the initial public comments are available at:

<https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=282&ExpandComments=n&bc=ACAAAAAAAgAAAA%3d%3d&>

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under § 1862(l)(6) of the Act. In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage. Moreover, in most circumstances, the item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)). The Supreme Court has recognized that “[t]he Secretary’s decision as to whether a particular medical service is ‘reasonable and necessary’ and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions.” *Heckler v. Ringer*, 466 U.S. 602, 617 (1984). See also, 78 Fed. Reg. 48,164, 48,165 (August 7, 2013)

When making national coverage determinations, we consider whether the evidence is relevant to the Medicare beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully consider the demographic characteristics and comorbidities of study participants as well as the provider training and experience. This section of the proposed decision provides an analysis of the evidence, which included the published medical literature and guidelines pertaining to gender dysphoria, that we considered during our review to answer the question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

A. Analysis

1. Study Demographics

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These studies were conducted in a total of 13 countries. Most were conducted in Europe (a total of 24 in Europe: Belgium four, Germany four, Ireland one, Italy one, Japan one, Sweden four, Switzerland one, United Kingdom three [not including the Barrett, 1998 study and the duplicative Megeri, Khoosal, 2007 study], and Yugoslavia one). One was in Asia (Singapore); one in South America (Brazil). Seven were conducted in North America (U.S. six, Canada one). One of the North American studies was a U.S.-conducted internet survey with non-U.S. and U.S. participants with a sub-analysis of the U.S. patients (Newfield et al., 2006).

All of the studies, with the exception of a national-wide mortality study (Dhejne et al., 2011), the international internet survey (Newfield et al., 2006), and the internet/convention site survey (Ainsworth, Spiegel, 2010), were conducted with patient populations from single sites. Many of these clinical centers cited in these studies were specialized tertiary referral centers offering comprehensive, integrated (psychiatric-psychological, endocrine, and surgical) care and whose staff could have been involved in both the patient care and the study. Of the studies reviewed, the Lawrence, 2006 study was conducted by a physician psychologist who surveyed the patient population of a single U.S. surgeon. The Ainsworth, Spiegel, 2010 study was conducted by a U.S. otolaryngologist with extensive surgery training who assessed the impact of facial feminization on transgender patients. The Hess et al. 2014 study was undertaken at a German university urologic specialty clinic. The Wolfradt, Neumann, 2001 study was conducted in Germany by a university otorhinolaryngologist and psychologist on patients who had undergone vocal cord surgery after reassignment surgery. The Rupp, Pfafflin 2015 study was undertaken by investigators who had seen the patients in a German forensic psychotherapy clinic.

2. Patient Population

Demographic assessments of the studies revealed that the mean ages of participants were in the 20s and 30s. (See Appendix C and Appendix D). Even when including standard deviation, most patients included in the study were under the age 60. Age of participants in the reviewed studies is important to assess generalizability to the Medicare population which is comprised predominantly of adults' age 65 years and older. While certain younger disabled adults are included in Medicare, generalizability of studies performed outside in the U.S. is likely reduced further since criteria to determine disability is unique to Medicare. When reporting ages of patients participating in studies, studies included mean age of population, but often failed to reveal standard deviation of the population. Most studies reported pre and post gender reassignment surgery ages, though some studies only reported post-surgery ages (Dehjne, 2011; Kuhn et al., 2009; Rakic et al., 1996; Rupp, Pfafflin, 2015; Udeze et al., 2008; Megeri, Khoosal, 2007; Wolfradt, Neumann, 2001; Blanchard et al., 1985; Weyers et al., 2009; Wierckx et al., 2011; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Salvador et al., 2012; Tsoi, 1993).

There was extensive lack of study participation and loss to follow-up in the published studies. (See Appendix C and Appendix G). This suggests that the population that seeks evaluation/treatment for gender dysphoria and/or applies for reassignment surgery is not the same population that undergoes reassignment surgery without hesitation or regret. The notable numbers of incomplete questionnaires similarly raises questions. This selection bias limits generalizability of any results.

3. Study Design

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As noted earlier, a number of research designs were found when exploring the question, "Does gender reassignment surgery improve health outcomes?" (Mate-Kole et al., 1990) (see Figure 1). Two of the studies were blinded. (Hess, 2014; Lawrence, 2006) A total of 29 studies were not blinded. The blinding status of the two internet surveys is unknown (Ainsworth, Spiegel, 2010; Newfield et al., 2006).

Observational studies can be prospective, retrospective, or have components of both. But each observational study design has limitations, and may not be able to show the true association between gender/reassignment surgery and improved health outcomes. Limitations of observational studies include that they frequently generate unreliable findings, and they also generate bias; because of confounding, causal inferences cannot reliably be drawn. Thus these types of studies are limited in terms of evidentiary weight. Only a true experimental study (e.g., randomized clinical trial) has the potential to demonstrate a causal relationship between two factors.

In general, one of the advantages of prospective studies is that they could potentially help determine factors associated with improved outcomes due to their longitudinal observation over time, and the collection of results at regular time intervals minimizes recall error. However, retrospective studies have problems including: some key statistics cannot be measured, significant biases including selection bias, recall bias, and information bias may limit a retrospective study's applicability. Another problem with retrospective studies is that the temporal relationship between variables is frequently difficult to assess. Finally, it is difficult to control exposure or outcome assessment in a retrospective study design.

Studies that use controls as part of its research design have higher evidentiary weight than studies that lack controls. That is because the use of controls can help to eliminate the possibility of confounding. But controls by themselves are no guarantee of complete validity. In terms of the use of controls in these studies that we evaluated some studies had no concurrent controls; some studies used control groups, but they were not concurrent; some studies used semi-matched controls; and in other studies patients served as their own controls.

Seventeen observational studies, of which 10 used longitudinal and 7 used cross-sectional study designs, had formal control groups. In this group of studies, the cross-sectional studies used various controls including healthy volunteers and patients with other disorders or treatments. In this same group of studies, the longitudinal studies used various controls including the patients as their own serial control, other treatment groups in addition to having patients serve as their own controls, and control cohorts derived from national databases. Among the longitudinal studies with used patients as their own controls, 4 used self-report test instruments that were validated in large populations. Of these 4, 1 had more than 100 subjects, self-reported and others, or other cohorts using either national data or national registries. Some observational studies included in this analysis had surgery-only populations and used no controls, or used indirect controls incorporating normative testing. The remainder of the observational studies had mixed populations that included surgical patients and patients using other treatments or patients treated with non-genital gender reassignment surgical procedures. The studies that included groups with mixed populations either had no controls, or used indirect controls (statistical methods included ANOVA, correlation, or regression).

Our review included 25 prospective studies. Of these prospective studies, two used a retrospective approach to acquire data for a single parameter (Eldh et al., 1997; Johansson et al., 2009); one prospective study used a retrospective approach to acquire data for several parameters (Ruppin, Pfafflin, 2015); and one study used a
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We found three retrospective studies (Asscheman et al., 2011; Dhejne et al., 2011; Landen et al., 1998). One study had at least a partially retrospective component, but with insufficient information to determine whether any of the data were obtained prospectively (Haraldsen, Dahl, 2000).

There were 11 longitudinal studies (Asscheman et al., 2011; Dhejne et al., 2011; Heylens et al., 2014; Kockott, Fahrner, 1987; Landen et al., 1998; Mate-Kole et al., 1979; Rakic et al., 1996; Rupp, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008). Ten of the longitudinal studies occurred in the group of studies with a designated control group (all of the above with the exception of Asscheman et al., 2011). In seven of the 11 longitudinal studies, the patients served as their own control over time before and after surgery (Heylens et al., 2014; Kockott, Fahrner, 1987; Meyer, Reter, 1979; Rakic et al., 1996; Rupp, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008).

There were 19 cross-sectional studies (Ainworth, 2010; Haraldsen, Dahl, 2000; Beatrice, 1985; Kraemer et al., 2008; Kuhn et al., 2009; Mate-Kole et al., 1988; Wolfradt, Neumann, 2001; Blanchard et al., 1985; Weyers et al., 2009; Wierckx et al., 2011; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Salvador et al., 2012; Tsoi, 1993; Gómez-Gil et al., 2012; Hepp et al., 2005; Motmans et al., 2012; Newfield et al., 2006; Gómez-Gil et al., 2013; Johansson et al., 2009; Leinung et al., 2013). Of this number, two were cross-sectional with the exception of data collection for aspects of a single parameter that had occurred in the past (Eldh et al., 1997; Johansson et al., 2009), and one study asked participants to recall the status of a parameter prior to treatment (Wierckx et al., 2011a).

Seventeen of the studies had explicit control groups. Of the studies with explicit control groups, two studies derived controls from national databases (Dhejne et al., 2011 and 2014; Landen et al., 1998); five studies used the patients themselves as longitudinal controls (Heylens 2014a; Rakic et al. 1996; Rupp, Pfafflin, 2015; Smith et al., 2005a; Udeze et al., 2008; Megeri 2007); eight used various other controls (Ainsworth, Spiegel, 2010; Beatrice 1985; Haraldsen, Dahl, 2000; Kraemer et al., 2008; Kuhn et al., 2009; Mate-Kole et al., 1988 and 1990; Wolfradt, Neumann, 2001); and two studies used both treatment-type cohorts and patients themselves as controls (Kockott, Fahrner, 1987; Meyer, Reter 1979).

A number of studies consisted of surgical series, but in these studies there were no concurrent controls (Wierckx et al., 2011; Salvador et al., 2012; Blanchard et al., 1985; Tsoi, 1993; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Weyers, 2009a). In three surgical series normative data from psychometric instruments were used as the control (Blanchard et al., 1985a; Weyers 2009a; Wierckx et al., 2011b). In five surgical series, controls were lacking (except for the use of serial employment data in the Eldh et al. 1997 study) (Eldh et al., 1997; Hess 2014; Lawrence 2006; Salvador 2012; Tsoi, 1993).

Patients underwent a variety of surgical interventions in five studies. There were no controls. The role of surgical

As mentioned in previous paragraphs, some prospective studies included in this analysis were cross-sectional in nature, and consisted of treated cohorts using a normative test, or a treatment cohort along with volunteer healthy cohorts. However, as we have noted, cross-sectional studies also have their limitations, including inability to determine temporal relationship between exposure and outcome (lacks time element). In other words, findings noted in a cross-sectional design cannot be inferred, because only current health and exposure to interventions are being studied. Also measurement error is an issue. Longitudinal studies with controls are most appropriate for determining this relationship between exposure and outcomes.

Observational studies have limitations. The lack of blinding has the potential to interfere with patient reported outcomes, which by their nature are subjective. Observational studies are prone to selection bias. Patients who seek treatment may not be the same as those who complete treatment-particularly if there are serial steps in the treatment process. (See Appendix G) Cross-sectional studies are prone to confounding. The impact of a particular step in a multi-faceted treatment process cannot be ascertained. The lack of a control group does not permit attribution of any outcome change to a specific intervention. There were seven studies where the patients themselves serve as longitudinal controls. The lack of a control makes it difficult to assess the results because there is not another group to make comparisons.

4. Psychometric Measurement Tools

There is also myriad use of measurement tools to assess patients suffering with gender dysphoria. (See Appendix E for a list of Psychometric Measurement tools.)

Some of the domains addressed in psychometric measurement tools measure the degree of depression and anxiety, body imagery, quality of life, identity traits, general wellbeing, physical and psychological function, self-concept, and others. Some of these measurement tools have been validated for patients with this condition, while others have been validated for other medical conditions. Some of the measurement tools found in this assessment were self-developed and there is no mention of validity when trying to determine if the test reliably measures what it is intended to measure.

5. Study Endpoints

A wide variety of study endpoints were used. Endpoints were collected from a number of sources, including self-reporting, clinician assessment, and medical records as well national databases. Some of the endpoints included
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patient reported quality of life (QOL) as manifest by psychometric testing, sense of well-being, body imagery, anxiety and depression, sexual function and fertility function, and social function. Objective endpoints included employment status, psychiatric function, and morbidity and mortality as well as adverse events.

Thirty of the studies employed 31 psychometric tools or investigator designed self-report surveys. (See Appendix E) Twenty investigators designed their own measurement tools or modified those of others.

External information on test validity, the size/composition of the reference population(s), diagnostic cut-points, and scoring was often not available because it was unpublished, proprietary, or in a non-English language. Six of the instruments, all non-specific, (the European QOL Survey, MMPI, SF-36, SCL-90, TSCS, and WHO-QOL-BREF), appear to have substantive normative data for comparative scoring (i.e., reference populations (≥ 1000) and obtained through representative sampling). Although these tools had been validated in a reference population, none had been validated in populations with gender dysphoria. Furthermore the investigators did not provide diagnostic cut-points and did not pre-specify the magnitude of test score change or test score difference considered to be biologically significant so the clinical importance could not be easily ascertained.

Only four investigator groups used only these psychometric tools validated in other large populations as their test instrument (Beatrice, 1985; Haraldsen, Dahl, 2000; Motmans et al., 2012; Newfield et al., 2006). Nine investigator groups used a mix of psychometric tools validated in large normative populations, less well validated tools, and/or self-designed tools (Ainsworth, Spiegel, 2010; Blanchard et al., 1985a; Gomez-Gil et al., 2014; Heylens 2014a; Ruppín, Pfafflin, 2015; Smith et al., 2005a (Udeze et al., 2008; Megeri 2007; Weyers 2009a; Wierckx et al., 2011b). Nine investigators used self-designed tools as their only test instrument (Eldh et al., 1997; Hess 2014; Johansson et al., 2009; Kockott, Fahrner, 1987; Lawrence, 2006; Meyer, Reter 1979; Rakic 1996; Salvador 2012; Tsoi 1993). A single investigator did not use any type of testing tool and provided only descriptive statistics (Leinung et al., 2013).

Three studies reported on complications linked or possibly linked to hormone treatment (Asscheman et al., 2011; Dhejne et al., 2011; Leinung et al., 2013), six studies reported on complications from reassignment surgery (Eldh et al., 1997; Lawrence, 2006; Ruppín, Pfafflin, 2015; Smith et al., 2005; Weyers et al., 2009; Wierckx et al., 2011). One study reported on serious and formalized regret for undergoing reassignment surgery (Landen et al., 1998), and one study reported on a patient with suicidal ideation who requested phallus removal (Meyer, Reter, 1979). Others reported on less severe or less formalized levels of regret. Five studies reported on the treatment or diagnosis of psychiatric disease (Dhejne et al., 2011; Haraldsen, Dahl, 2000; Hepp et al., 2005; Landen et al., 1998; Leinung et al., 2013; Meyer, Reter, 1979; Ruppín, Pfafflin, 2015; Udeze et al., 2008). Two studies reported on the history of psychiatric disease in their patient populations (Matte-Kole, 1988; Matte Kole, 1990).

Four studies reported on suicide attempts (Dehjne et al., 2011; Eldh et al., 1997; Heylens et al., 2013; Kockott, Fahrner, 1987), two studies reported on the history of suicide attempts in their patient population (Matte-Kole, 1988; Matte Kole, 1990). Three studies reported on suicide, of which one of them occurred incidentally (Asscheman et al., 2011; Blanchard et al., 1985; Dhejne et al., 2011). Two studies also reported on mortality (Asscheman et al., 2011; Dhejne et al., 2011).

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There was a great degree of inconsistency in endpoints. Also endpoints were collected from a number of sources, including self-reporting, clinical assessment, and medical records as well as national databases. Endpoints lacked operational definitions thus making their applicability difficult. CMS is interested in knowing what patients diagnosed with gender dysphoria believe are important endpoints that should be studied.

Mortality and Regret as Endpoints

Certain kinds of objective outcomes can be assessed by other types of study designs-albeit somewhat less robust. These include mortality and regret (as manifest by request for surgical reversal) when the data are rigorously prospectively collected in a comprehensive registry for all patients who have met specified entry criteria and treatment criteria.

More specifically, Swedish investigators extracted data from registries at the National Board of Health and Welfare to which all patients seeking reassignment surgery or reversal of reassignment surgery must make formal application. In the initial 1998 study, of the 233 applicants for reassignment surgery between July 1972 and June 1992, 20 were denied surgery, and subsequently 13 (3.8%) surgical patients requested return to the natal sex (Landen et al., 1998). In the 2014 follow-up study, of the 767 applicants for reassignment surgery or a change in legal status after surgery between 1960-2010, 86 were denied, and subsequently 15 (2.2%) requested reversal to the natal gender (Dhejne et al., 2014). Although the data from the two studies are not directly comparable because of the much shorter follow-up period in the latter study and although the analyses also did not consider other possible expressions of regret including suicide, the studies suggest that the majority of highly vetted patients in a structured care system do not express regret as defined by a formal request for return to natal gender status (Dhejne et al., 2011). The study, however, cannot assess the impact of gender reassignment surgery per se because of the confounding introduced by the other interventions.

Swedish investigators also conducted the most comprehensive study with functional endpoints of the 33 studies reviewed. This study relied on compulsory national databases (Dhejne et al., 2011) tracked all patients who had undergone reassignment surgery (at a mean age 35.1 years) over a 30 year interval and compared them to 6480 matched controls from the general population. They identified both increased mortality and increased psychiatric hospitalization. The mortality was primarily due to completed suicides (19.1-fold greater), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. The divergence in mortality from the Swedish population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in control Swedes even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the sex of the control. For the same reasons as delineated above, this study cannot assess the impact of gender reassignment surgery per se because of the confounding introduced by the other interventions. The finding of this study demonstrated that reassignment surgery does not return patients to a normal level of morbidity risk and that the morbidity risk is significant even in highly vetted patients in a structured care system.

B. Discussion

Gender dysphoria by the latest and prior nomenclature is a state in which there is incongruence between the gender assigned at birth and the gender(s) with which the person identifies. This incongruence may result in varying degrees of discontent and distress. Satisfaction and quality-of-life are well recognized as "latent variables" (hypothetical constructs) which cannot be measured directly (Borsboom et al., 2003; Newsom, 2015). As such, observable entities are used to infer or approximate satisfaction and/or quality-of-life. It may be challenging to identify parameters that truly reflect the nature and the magnitude of dysphoria in the individual. This challenge is followed by the need to know to what extent a specific test measures that which it purports to measure (test validity) and whether repeat testing will yield a comparable answer (test reliability).

The investigators of the clinical research reviewed in this NCD have attempted to measure dysphoria levels by objective data elements and by use of various psychometric and function scales/surveys. The objective data elements include a number of variables such as employment, morbidity, and formal requests for surgical reversal.

The psychometric tools used to assess outcomes have limitations. Many of the instruments that are most specific for the condition were designed by the investigators themselves or by other investigators in the field. In addition, the relevant diagnostic cut-points for scores and changes in scores that are clinically significant should be delineated to permit adequate interpretation of test results. As such, these studies were not definitive in nature.

Other factors might impact the utility of a given test. Patients undergo serial evaluations and a sequence of treatments (Bockting et al., 2011). These other interventions may reduce internal validity of the test. The affirmation and support obtained in psychotherapy-psychiatric care, the adjustment confidence gained in real life cross-gender behavior, and/or the physical and mental changes from hormone therapy may be (an) alternative cause(s) of the findings. Several studies suggest that there is a major therapeutic benefit from hormone therapy (Colizzi et al., 2013; Gómez-Gil et al., 2011; Gorin-Lazard et al., 2011, 2013; Heylens et al., 2014; Dubois, 2012). Another suggests that there is therapeutic benefit from time in the preferred gender role without other intervention (Greenberg, Laurence, 1981). As such, results from cross-sectional studies may be misleading. None of the studies used adequately matched controls over time. We believe longitudinal studies with serial assessment of the same patients would provide more robust answers. We note that even from the results from the four studies in which patients served as their own controls and which used an instrument known to be validated in large populations were negative (i.e., there was no improvement in psychometric or quality of life outcomes when patients were tested just prior to and at some point after the reassignment surgical intervention). (Heylens, 2014; Ruppín, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008). Further, rigorous studies with the use of appropriate comparison patients could better clarify the specific benefits and harms of each of the interventions.

CMS reviewed and considered potential objective measures of function including mortality, psychiatric treatment, and attempted suicide. None of the longitudinal studies in which patients served as their own control, however, comprehensively tracked changes in these events as objective measures of function before and after surgery. Events such as suicide and institutionalization were mentioned incidentally when describing patients excluded from a follow-up study or during the study (Heylens et al., 2014; Ruppín, Pfafflin, 2015). Other times investigators tracked these functional outcomes (e.g., psychiatric out-patient treatment, psychiatric in-patient treatment, and substance abuse) for the most current prior year (Ruppín, Pfafflin, 2015).

The most comprehensive study with functional endpoints, the Swedish study that followed all patients who had undergone reassignment surgery (at mean age 35.1 years) over a 30 year interval and compared them to 6480 matched controls, identified increased mortality and increased psychiatric hospitalization (Dhejne et al., 2011). The mortality was primarily due to completed suicides (19.1-fold greater than in control Swedes), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. The divergence in mortality from the Swedish population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in controls even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the gender of the control. Unfortunately, the study was not constructed to assess the impact of gender reassignment *per se*. The finding of this study, again, demonstrated that reassignment surgery does not return patients to a normal level of morbidity risk and that the morbidity risk is significant, because of its clinical importance, its persistence over the interval of data collection and the increase in risk over time for the individual.

1. Patient Care

Additional questions regarding the care of patients with gender dysphoria remain. The specific type(s) of gender/sex reassignment surgery (genital, non-genital) that could improve health outcomes in adults remain(s) uncertain because most studies included patients who had undertaken one or more of a spectrum of surgical procedures or did not define the specific surgical procedures under study. Furthermore, most studies did not assess specific surgical procedures except for technical aspects. Surgical techniques have changed significantly over the last 60 years (Bjerrome Ahlin et al., 2014; Doornaert, 2011; Green, 1998; Pauly, 1968; Selvaggi et al., 2007; Selvaggi, Bellringer, 2011; Tugnet et al., 2007; Doornaert, 2011).

The WPATH care recommendations presented a general framework and guidance on the care of transgender individual. The standards of care are often cited by entities that perform gender reassignment surgery. WPATH noted: "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria." Appendix D in the WPATH Standards of Care acknowledged the historical problems with evidentiary standards, the preponderance of retrospective data, and the confounding impact of multiple interventions, specifically distinguishing the impact of hormone therapy from surgical intervention.

The surgical expertise and care setting(s) required to improve health outcomes in adults with gender dysphoria remain(s) uncertain. The selection of a particular surgeon could become an important variable if subjective outcomes depend on functional surgical results (Ross 1989). Many of these procedures involve complicated gynecologic, urologic surgical techniques accompanied by significant risk (Goddard et al., 2007a; Kuhn et al., 2011; Lawrence, 2003; Leclere et al., 2015; Rachlin, 1999; Rupp, Pfafflin, 2015). Most of the studies for reassignment surgery have been conducted in northern Europe at select centers with integrated care (psychological, psychiatric, endocrinologic, and surgical) in which there is sequential evaluation of patients for progressively more invasive interventions.

Additionally, CMS met with several stakeholders and conducted several interviews with centers that focus on healthcare for transgender individuals in the U.S. Primary care was often the centers' main focus rather than

2. Generalizability

With the variability in the study participants, providers and settings, the generalizability of the studies reviewed to the Medicare population is unclear. Many of the studies are old since they were conducted more than 10 years ago. Many of the programs were single-site centers without replication elsewhere. Most of these studies were conducted outside of the U.S. with far different medical systems for treatment and follow-up. The study populations were young and without significant physical or psychiatric co-morbidity. As noted above psychiatric co-morbidity may portend poor outcomes (Asscheman et al., 2011; Landen et al., 1998).

For the above reasons, it is difficult to generalize these studies to the Medicare population.

3. Knowledge Gaps

This patient population faces complex and unique challenges. The medical science in this area is evolving. There are, however, many gaps in the evidentiary base. These gaps have been delineated because they represent areas in which patient care can be optimized and which are opportunities for much needed research.

The Institute of Medicine, the National Institutes of Health, and others have delineated many of the gaps in the data. (Boehmer, 2002; HHS-HP, 2011; IOM, 2011; Kreukels-ENIGI, 2012; Lancet, 2011; Murad et al., 2010; NIH-LGBT, 2013) The current or completed studies listed in ClinicalTrials.gov are not structured to assess these gaps.

The currently available evidence has limitations:

- There were design deficiencies. All but one of the studies were observational in nature. All but two were non-blinded. The accompanying loss to follow-up suggests that there is selection bias and that the population that seeks treatment for gender dysphoria is not the same population that undergoes reassignment surgery without hesitation or regret.
- The psychometric and psychosocial function endpoints are not well validated.

- There were limitations of the psychosocial endpoints and of the data collection of other hard functional outcomes. Evidence on mortality and especially suicide was stronger. The mortality and psychiatric hospitalization rates even after vetting in highly structured programs are of concern.
- There are insufficient data to select optimal candidates for surgery.
- The results were inconsistent, but negative in the best studies, i.e., those that reduced confounding by testing patients prior to and after surgery and which used psychometric tests with some established validation in other large populations. (Atkins et al., 2004; Balshem et al., 2011; Chan, Altman, 2005; Deeks et al., 2003; Guyatt et al., 2008a-c; 2011a-e; Kunz, Oxman, 1998; Kunz et al., 2007 and 2011; Odgaard-Jensen et al., 2011).
- Data on reassignment surgery performed on geriatric patients or follow-up data in geriatric patients who had reassignment surgery in the distant past is anecdotal (Orel, 2014).

C. Health Disparities

Four studies included information on racial or ethnic background. The participants in the 3 U.S. based studies were predominantly Caucasian (Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006). All of the participants in the single Asian study were Chinese (Tsoi, 1993). Additional research is needed in this area.

D. Summary

Based on a thorough review of the clinical evidence available at this time, there is not enough evidence to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria. There were conflicting (inconsistent) study results – of the best designed studies, some reported benefits while others reported harms. The quality and strength of evidence were low due to the mostly observational study designs with no comparison groups, potential confounding and small sample sizes. Many studies that reported positive outcomes were exploratory type studies (case-series and case-control) with no confirmatory follow-up. Due in part to the generally younger and healthier study participants, the generalizability of the studies to the Medicare population is also unclear. Additional research is needed. This proposed conclusion is consistent with the West Midlands Health Technology Assessment Collaboration (2009) that reported “[f]urther research is needed but must use more sophisticated designs with comparison groups.” WPATH also noted the need for further research: “More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria.” Further, as mentioned earlier, patient preference is an important aspect of any treatment. With that in mind, CMS is interested in knowing from the patients with gender dysphoria what is important to them as a result of a successful gender reassignment surgery.

Knowledge on gender reassignment surgery for individuals with gender dysphoria is evolving. The specific role for various surgical procedures is less well understood than the role of hormonal intervention. Much of the available research has been conducted in highly vetted patients at select care programs integrating psychotherapy, endocrinology, and various surgical disciplines and operating under European medical management and regulatory structures. Standard psychometric tools need to be developed and tested in the patients with gender dysphoria to validly assess long term outcomes. As such, further evidence in this area would contribute to the question of whether gender reassignment surgery improves health outcomes in adults with gender dysphoria.

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Because CMS is mindful of the unique and complex needs of this patient population and because CMS seeks sound data to guide proper care of the community based on the patient population, CMS strongly encourages robust clinical studies with adequate patient protections that will fill the evidence gaps delineated in this decision memorandum. As the Institute of Medicine (IOM, 2011) importantly noted: "Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

IX. Proposed Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

In the absence of a NCD, initial coverage determinations under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements will be made by the local Medicare Administrative Contractors (MACs) on an individual claim basis.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform the answer to the question posed in this proposed decision memorandum. Based on the gaps identified in the clinical evidence, these studies should focus on which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be developed that would support coverage with evidence development (CED), which would only cover gender reassignment surgery for beneficiaries who choose to participate in a clinical study.

X. Appendices

A. Appendix A

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III 1980 <i>Chapter: Psychosexual Disorders</i>	Trans-sexualism 302.5x [Gender Identity Disorder of Child-hood (302.6)]	Required A (cross- gender identification) and B (aversion to one's natal gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	Sense of discomfort and inappropriateness about one's anatomic sex. Wish to be rid of one's own genitals and to live as a member of the other sex. The disturbance has been continuous (not limited to periods of stress) for at least 2 years.	Further characterization by sexual orientation Distinguished from Atypical Gender Identity Disorder 302.85
DSM III- Revised 1987 <i>TS classified as an Axis II dx (personality disorders and mental retardation) in a different chapter. GID included under Disorders Usually First Evident in Infancy, Childhood, Adolescence</i>	Trans-sexualism (TS) (302.50) [GID of C]	Required A and B criteria	Persistent discomfort and sense of inappropriateness about one's assigned sex. Persistent preoccupation for at least 2 years with getting rid of one's 1° and 2° sex characteristics and acquiring the sex characteristics of the other sex. Has reached puberty	Further characterization by sexual orientation Distinguished from Gender Identity Disorder of Adolescence or Adulthood, Non-trans- sexual Type •e.g., cross-dressing not for the purposes of sexual excitement Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions Gender Identity Disorder Not Otherwise Specified 302.85 •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
	GID of adulthood , non- trans-sexual type, added			
DSM IV 1994 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder in Adolescents and Adults (302.85) (Separate criteria & code for children, but same name)	Required A and B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., Stated desire to be another sex •e.g., Desire to live or be treated as a member of the other sex •e.g., conviction that he/she has the typical feelings and reactions of the other sex •e.g., frequent passing as the other sex Persistent discomfort with his/her sex or sense of inappropriateness in the gender role of that sex. •e.g., belief the he/she was born the wrong sex	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex

DSM Version	Condition Name	Criteria	Criteria	Comments
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			<ul style="list-style-type: none"> •e.g., preoccupation with getting rid of 1^o and 2^o sex characteristics &/or acquiring sexual traits of the other sex •Clinically significant distress or impairment in social, occupational, or other important areas of functioning 	
DSM IV-Revised 2000 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder (Term trans-sexual-ism eliminated)	Required A & B criteria Dx excluded by physical intersex condition	Cross-gender identification <ul style="list-style-type: none"> •e.g., stated desire to be the other sex •e.g., desire to live or be treated as the other sex •e.g., conviction that he/she has the typical feelings & reactions of the other sex •e.g., frequent passing as the other sex Persistent discomfort with his or her sex OR sense of inappropriateness in the gender role of that sex <ul style="list-style-type: none"> •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1^o and 2^o sex characteristics &/or acquiring sexual traits of the other sex Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Outcome may depend on time of onset Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 <ul style="list-style-type: none"> •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM V 2013 <i>Separate Chapter from Sexual Dysfunctions & Paraphilic Disorders</i>	Gender Dysphoria (302.85)	Gender nonconformity itself not considered to be a mental disorder The dysphoria associated with the gender incongruence is Eliminates A & B criteria Considers gender incongruence to be a spectrum Considers intersex/ "disorders of sex development" to be a subsidiary and not exclusionary to dx of GD	<ul style="list-style-type: none"> •Marked discordance between natal 1^o and 2^o sex characteristics* and experienced/expressed gender •Conviction that he/she has the typical feelings & reactions of the other sex (or some alternative gender) •Marked desire to be the other sex (or some alternative gender) •Marked desire to be treated as the other sex (or some alternative gender) •Marked desire to be rid of natal 1^o and 2^o sex characteristics** •Marked desire to acquire 1^o and 2^o sex characteristics of the other sex (or some alternative gender) Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Includes diagnosis for post transition state to permit continued treatment access Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity syndromes

DSM Version	Condition Name	Criteria	Criteria	Comments
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			<p>* or in young adolescents, the anticipated 2° sex characteristics</p> <p>** or in young adolescents, prevent the development of the anticipated 2° sex characteristics</p> <p>≥ 6 month marked discordance between natal gender & experienced/expressed gender as demonstrated by ≥ 6 criteria:</p> <ul style="list-style-type: none"> •Strong desire to be of the other gender or an insistence that one is of another gender. •Strong preference for cross-gender roles in make-believe play. •Strong preference for the toys, games, or activities of the other gender. •Strong preference for playmates of the other gender. •In boys, strong preference for cross-dressing; in girls, strong preference for wearing masculine clothing •In boys, rejection of masculine toys, games, activities, avoidance of rough and tumble play; in girls, rejection of feminine toys, games, and activities. 	
	Unspecified Gender Dysphoria (302.6) (F64.9)		This category applies to presentations in which sx c/w gender dysphoria that cause clinically significant distress or impairment, but do not meet the full criteria for gender dysphoria & the reason for not meeting the criteria is not provided.	
	Specified Gender Dysphoria 302.6 (F64.8)		If the reason that the presentation does not meet the full criteria is provided then this dx should be used	

C/W=consistent with Dx=diagnosis GD=gender dysphoria Sx=symptoms TS=transsexual 1°=primary
2°=secondary

B. Appendix B

1. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
 Non-randomized controlled trials
 Prospective cohort studies
 Retrospective case control studies
 Cross-sectional studies
 Surveillance studies (e.g., using registries or surveys)
 Consecutive case series
 Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

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The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix C

Patient Population: Enrolled & Treated with Sex Reassignment Surgery Loss of Patients & Missing Data

Panel A (Controlled Studies)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Dhejne 2011	Longitudinal Controlled	480 w GID who did not apply or were not approved for SRS were excluded	324	324 (100%)	-
Dhejne 2014 Landen	Longitudinal for test variable Controlled	767 applied for SRS 25 applications denied. 61 not granted full legal status 15 formal applications for surgical reversal	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper
Heylens	Longitudinal Controlled	90 applicants for SRS 33 excluded 11 later excluded had not yet received SRS by study close.	57 (46)	46 (80.7%) Only those w SRS evaluated	Psycho-social survey missing data for 3 at baseline & 4 after SRS. SCL90 not completed by 1 at baseline, 10 after hormone tx, & 4 after SRS missing data for another 1.1% to 11.1%.
Kockott	Longitudinal Controlled	80 applicants for SRS 21 excluded	59	32 (54.2%) went to surgery	1 preoperative patient was later excluded b/c lived completely in aspired gender w/o SRS. Questions on financial sufficiency not answered by 1 surgical patient.

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
					Questions on sexual satisfaction & gender contentment not answered by 1 & 2 patients awaiting surgery respectively.
Mate-Kole 1990	Longitudinal Controlled	40 sequential patients of accepted patients. The number in the available patient pool was not specified.	40	20 (50%) went to surgery	-
Meyer	Longitudinal Controlled	Recruitment pool: 100 52 excluded.	50	15 (30%) had undergone surgery 14 (28%) underwent surgery later	The assessments of all were complete
Rakic	Longitudinal Controlled	92 were evaluated 54 were excluded from surgery 2 post SRS were lost to follow-up 2 post SRS were excluded for being in the peri-operative period	32	32 (100%)	Questionnaire completed by all.
Ruppin	Longitudinal Controlled	The number in the available patient pool was not specified. 140 received recruitment letters. 69 were excluded	71	69 (97.2%)	The SCL-90, BSRI, FPI-R, & IPP tests were not completed by 9, 34, 13, & 16 respectively. Questions about romantic relationships, sexual relationships, friendships, & family relationships were not answered by 1, 3, 2, & 23 respectively. Questions regarding gender security & regret & were not answered by 1 & 2 respectively.
Smith	Longitudinal Controlled	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. 103 were excluded from additional tx	162	162 (100%)	36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete various post-SRS tests.
Udeze Megeri	Longitudinal Controlled	International patient w GD 546 & post SRS 318. 40 M to F subjects were prospectively selected.	40	40 (100%)	-
Ainsworth	Internet/convention Survey Cross-sectional Controlled	Number of incomplete questionnaires not reported	247	72 (29.1%) 75 (30.6%) facial 147 (59.5%) had received neither facial nor reassignment surgery	-
Beatrice	Cross-sectional		40	10 (25%)	App. 657

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	Controlled	14 excluded for demographic matching reasons			The assessments were completed by all
Haraldsen	Cross-sectional Controlled	Recruitment pool: 99	86	59 (68.6%)	-
Kraemer	Cross-sectional Controlled	The number in the available patient pool was not specified.	45	22 (48.9%)	-
Kuhn	Cross-sectional Controlled	The number in the available patient pool was not specified.	75	55 (73.3%)	-
Mate-Kole 1988	Cross-sectional Controlled	150 in 3 cohorts. Matched on select traits. The number in the available patient pool was not specified.	150	50 (66.7%)	-
Wolfradt	Cross-sectional Controlled	The number in the available patient pool was not specified.	90	30 (33.3%)	-

Panel B (Surgical Series: No Concurrent Controls)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Blanchard et al.	Cross-sectional Control: Normative test data	294 clinic patients w GD had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded	79	79(100%)	-
Weyers et al.	Cross-sectional Control: Normative test data	>300 M to F patients had undergone GRS 70 eligible patients recruited 20 excluded	50	50 (100%)	SF-26 not completed by 1
Wierckx et al.	Cross-sectional except for recall questions Control: Normative test data	79 F to M patients had undergone GRS & were recruited. 3 additional non-clinic patients were recruited by other patients. 32 excluded initially; 1 later.	49	49 (100%)	SF-36 test not completed by 2. Questions regarding sexual re-lationship, sex function, & surgical satisfaction were answered by as few as 27, 28, 32 respectively.
Eldh et al.	Cross-sectional except for 1 variable Control: Self for 1 variable-employment	136 were identified. 46 excluded	90	90 (100%)	Questions regarding gender identity, sex life, acceptance, & overall satisfaction were not answered by 13, 14, 14 & 16 respectively. Employment data missing for 11.
Hess et al.	Cross-sectional		119	119 (100%)	App. 658

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Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No control	254 consecutive eligible patients post GRS identified & sent surveys. 135 excluded.			Questions regarding the esthetics, functional, and social outcomes of GRS were not answered by 16 to 28 patients.
Lawrence	Cross-sectional No control	727 eligible patients were recruited. 495 were excluded	232	232 (100%)	-
Salvador et al.	Cross-sectional No control	243 had enrolled in the clinic 82 completed GRS 69 eligible patients were identified. 17 excluded.	52	52 (100%)	-
Tsoi	Cross-sectional No control	The number in the available patient pool was not specified.	81	81 (100%)	-

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Gómez-Gil et al. 2012	Cross-sectional No direct control: Analysis of variance	200 consecutive patients were recruited. 13 declined participation or were excluded for incomplete questionnaires.	187	79 (42.2%)	See prior box.
Hepp et al.	Cross-sectional No direct control: Analysis of variance	The number in the available patient pool was not specified.	31	7 (22.6%)	HADS test not completed by 1
Motmans et al.	Cross-sectional No direct control: Analysis of variance & regression	255 with GD were identified. 77 were excluded.	148 (140)	Not clearly stated. At least 103 underwent some form of GRS.	8 later excluded for incomplete SF-36 tests. 37 w recent GRS or hormone initiation were excluded from analysis of SF-36 results103.
Newfield et al.	Internet survey Cross-sectional No direct control: Analysis of variance	Number of incomplete questionnaires not reported 446 respondents; 384 U.S respondents 62 non-U.S. respondents excluded from SF-36 test results 8 U.S. respondents excluded	376 (U.S.)	139 to 150 (37.0-39.9%) in U.S.	-
Gomez-Gil et al. 2014	Cross-sectional No direct control: Analysis w regression	The number in the available patient pool was not specified. 277 were recruited. 25 excluded	252(193)	80 (41.4%) non-genital surgery	59 were excluded for incomplete questionnaires. See prior box.
Asscherman	Longitudinal		1331	1177 (88.4%)	-

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No analysis by tx status	The number in the available patient pool was not specified.			
Johansson et al.	Cross-sectional except for 1 variable No analysis by tx status except for 1 question	60 eligible patients 18 excluded.	42	32 (76.2% of enrolled & 53.3% of eligible) (genital surgery)	-
Leinung et al.	Cross-sectional No analysis by tx status	242 total clinic patients	242	91 (37.6%)	Employment status data missing for 81 of all patients

*Data obtained via a survey on a website and distributed at a conference

B/C=because

BSRI=Bem Sex Role Inventory

F=Female

FP-R=Freiberg Personality Inventory

GD=Gender dysphoria

GID=Gender identity disorder

HADS=Hospital Anxiety & Depression Scale

IPP=Inventory of Interpersonal Problems

M=Male

NA=Not applicable

SCL-90=Symptom Checklist-90

SF-36=Short Form 36

GRS=Sex reassignment surgery

Tx=Treatment

W/o=without

Appendix D

Demographic Features of Study Populations

Panel A (Controlled Studies)

Author	Age (years; mean, S.D., range)	Gender	Race
Ainsworth	Only reassignment surgery: 50 (no S.D.) Only facial surgery: 51 (no S.D.) Both types of surgery: 49 (no S.D.) Neither surgery: 46 (no S.D.)	247 M to F	-
Beatrice	Pre-SRS M to F: 32.5 (27-42), Post-SRS: 35.1 (30-43)	20 M to F plus 20 M controls	100% Caucasian

Author	Age (years: mean, S.D., range)	Gender	Race
Dehjne 2011	Post-SRS: all 35.1±9.7 (20-69), F to M 33.3±8.7 (20-62), M to F 36.3±10.1(21-69)	133 (41.0%) F to M, 191 (59.0%) M to F; ratio 1:1.4	-
Dhejne 2014 Landen	F to M SRS cohort: median age 27 M to F SRS cohort: median age 32 F to M applicants for reversal: median age 22 M to F applicants for reversal: median age 35	767 applicants for legal/surgical reassignment 289 (37.7%) F to M, 478 (62.3%) M to F; ratio 1:1.6 681 post SRS & legal change 252 (37.0%) F to M, 429 (63.0%) M to F; ratio 1:1.7 15 applicants for reversal 5 (33.3%) F to M, 10 (66.7%) M to F; ratio 1:2	-
Haraldsen	Pre-SRS & Post-SRS: F to M 34±9.5, F to M 33.3±10.0 Post-SRS cohort reportedly older. No direct data provided.	Pre & Post SRS 35 (40.7%) F to M, 51 (59.3%) M to F; ratio 1:1.5	-
Heylens	-	11 (19.3% of 57) F to M, 46 (80.7%); ratio 1:4.2 (80.7% underwent surgery)	-
Kockott	Pre-SRS (continued wish for surgery): 31.7±10.2 Post-SRS: 35.5±13.1	Pre-SRS (continued wish for surgery) 3 (25%) F to M, 9 (75%) M to F; ratio 1:3 Post SRS: 14 (43.8%) F to M, 18 (56.2%) M to F; ratio 1:1.3	-
Kraemer	Pre-SRS: 33.0±11.3, Post-SRS: 38.2±9.0	Pre-SRS 7 F to M (30.4%), 16 M to F (69.6%); ratio 1:2.3 Post-SRS 8 F to M (36.4%), 14 M to F (63.6%); ratio 1:1.8	-
Kuhn	All post SRS: median (range): 51 (39-62) (long-term follow-up)	3 (5.4%) F to M, 52 (94.5%) M to F; ratio 1:17.3.	-
Mate-Kole 1988	Initial evaluation: 34, Pre-SRS: 35, Post-SRS: 37	150 M to F	-
Mate-Kole 1990	Early & Usual wait SRS: 32.5 years (21-53)	40 M to F	-
Meyer	Pre-SRS: 26.7 Delayed, but completed SRS: 30.9 Post-SRS: 30.1	Pre-SRS: 5 (23.8%) F to M, 16 (76.2%) M to F; ratio 1:3.2 Delayed, but completed SRS: 1 (7.1%) F to M, 13 (92.9%) M to F; ratio 1:13 Post-SRS: 4 (26.7%) F to M, 11 (73.3%) M to F; ratio 1:2.8	86% Caucasian
Rakic	All: 26.8±6.9 (median 25.5, range 19-47), F to M: 27.8±5.2 (median 27, range 23-37), M to F: 26.4±7.8 (median 24, range 19-47).	10 (31.2%) F to M, 22 (68.8%) M to F; ratio 1:2.2	-
Ruppin	All: 47.0±10.42 (but 2 w/o SRS) (13.8±2.8 yrs post legal name change) (long-term follow-up) F to M: 41.2±5.78, M to F 52.9±10.82	36 (50.7%) F to M, 35 (49.3%) M to F; ratio 1:0.97	-
Smith	Time of surgical request for post-SRS: 30.9 (range 17.7-68.1) Time of follow-up for post-SRS: 35.2 (range 21.3-71.9)	Pre-SRS: 162: 58 (35.8%) F to M, 104 [64.2%] M to F; ratio 1:1.8 Post-SRS: 126: 49 (38.9%) F to M, 77 (61.1%) M to F; ratio 1:1.6	-
Udeze Megeri	M to F: 47.33±13.26 (range 25-80).	40 M to F	-
Wolfradt	Patients & controls: 43 (range 29-67).	30 M to F plus 30 F controls plus 30 M controls.	-

*Data obtained via a survey on a website and distributed at a conference SD=Standard deviation

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Blanchard et al.	F to M: 32.6, M to F w M partner preference: 33.2, F to M w F partner preference: 47.7 years	Post-GRS: 47 (45.6%) F to M, 56 (54.4%) M to F; ratio 1:1.19. In study: 38 (48.1%) F to M, 32 (40.5%) M to F w M partner preference, 9 (11.4%) M to F w F partner preference; ratio 1:0.8: 0.2	-
Weyers et al.	Post-GRS M to F: 43.1 ±10.4 (long-term follow-up)	50 M to F	-
Wierckx et al.	Time of GRS: 30±8.2 years (range 16 to 49) Time of follow-up: 37.1 ±8.2.4 years (range 22 to 54)	49 M to F	-
Eldh et al.	-	50 (55.6%) F to M, 40 (44.4%) M to F; ratio 1:0.8 There is 1 inconsistency in the text suggesting that these should be reversed.	-
Hess et al.	-	119 M to F	-
Lawrence	Time of GRS: 44±9 (range 18-70)	232 M to F	-
Salvador et al.	Time of follow-up for post-GRS: 36.28±8.94 (range 18-58) (Duration of follow-up: 3.8±1.7 [2-7])	52 M to F	-
Tsoi	Time of initial visit: All: 24.0±4.5, F to M: 25.4±4.4 (14-36), M to F: 22.9±4.6 (14-36). Time of GRS: All: 25.9±4.14, F to M: 27.4±4.0 (20-36), M to F: 24.7±4.3 (20-36).	36 (44.4%) F to M, 45 (55.6%) M to F; ratio 1:1.25	0% 100% Asian

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Gómez-Gil et al. 2012	W & W/O GRS: All: 29.87±9.15 (range 15-61), W/O hormone tx: 25.9±7.5, W current hormone tx: 33.6±9.1. (At hormone initiation: 24.6±8.1).	W/O hormone tx: 38 (56.7%) F to M, 29 (43.3%) M to F; ratio 1:0.8. W hormone tx: 36 (30.0%) F to M, 84 (70.0%) M to F; ratio 1:2.3. Post-GRS: 29 (36.7%) F to M, 50 (63.3%) M to F; ratio 1:1.7.	-
Hepp et al.	W & W/O GRS: 32.2±10.3	W & W/O GRS: 11 (35.5%) F to M; 20 (64.5%) M to F; ratio 1:1.8.	-
Motmans et al.	W & W/O GRS: All (n=140) : 39.9±10.2, F to M: 37.0±8.5, M to F: 42.3±10.4	W & W/O GRS: N=140 63(45.0%) F to M, 77 (55.0%) M to F; ratio 1:1.2 N=103 49 (47.6%) F to M; 54 (52.4%) M to F; ratio 1:1.1	-
Newfield et al.	W & W/O GRS: U.S.+ non-U.S. : 32.8±11.2, U.S. 32.6±10.8	W & W/O GRS: U.S.+ non-U.S.: F to M, 438, U.S.: F to M: 376	89% of 336 respondents Caucasian
Gomez-Gil, et al. 2014	W & W/O Non-genital GRS: 31.2±9.9 (range 16-67).		-

Author	Age (years: mean, S.D., range)	Gender	Caucasian
		W & W/O Non-genital GRS: 74 (38.3%) F to M, 119 (61.7%) M to F; ratio 1:1.6.	
Asscherman	Time of hormone tx: F to M: 26.1±7.6 (16-56), M to F: 31.4±11.4 (16-76)	Met hormone tx requirements: 365 (27.4%) F to M, 966 (72.6%) M to F; ratio 1:2.6. Post-GRS: 343 (29.1%) F to M, 834 (70.9%) M to F; ratio 1:2.4.	-
Johanssen	Time of initial evaluation: F to M: 27.8 (18-46), M to F 37.3 (21-60). Time of GRS: F to M: 31.4 (22-49), M to F 38.2 (22-57). Time of follow-up for post-GRS: F to M: 38.9 (28-53), M to F 46.0 (25-69) (Long-term follow-up)	Approved for GRS: 21 (35%) F to M, 39 (65%) M to F; ratio 1:1.9) Post GRS: 14 (43.8%) F to M; 18 (56.2%) M to F; ratio 1:1.3)	-
Leinung et al.	Time of hormone initiation : F to M: 27.5, M to F 35.5	W & W/O GRS: 50 (20.7%) F to M, 192 M to F (79.3%); ratio 1:3.8. Post-GRS: 32 F to M (35.2%); 59 (64.8%) M to F; ratio 1:1.8.	-

Appendix E

Psychometric and Satisfaction Survey Instruments

Instrument Name and Developer	Development and Validation Information
APGAR Family Adaptability, Partner-ship Growth, Affection, and Resolve <i>Smilkstein</i>	Published in 1978 Initial data: 152 families in the U.S. A "friends" component was added in 1983. Utility has challenged by many including Gardner 2001
Beck Depression Inventory <i>Beck, Ward, Mendelson, Mock, & Erbaugh</i>	Published initially in 1961 with subsequent revisions It was initially evaluated in psychiatric patients in the U.S.A. Salkind (1969) evaluated its use in 80 general outpatients in the UK. It is copyrighted and requires a fee for use
Bem Sex Role Inventory <i>Bem</i>	Published 1974 Initial data: 100 Stanford Undergraduates 1973 update: male 444; female 279 1978 update: 470; female 340
Body Image Questionnaire <i>Clement & Lowe</i>	Validity study published 1996 (German) Population: 405 psychosomatic patients, 141 medical students, 208 sports students
Body Image Scale <i>Lindgren & Pauly</i> <i>(Kuiper, Dutch adaptation 1991)</i>	1975 Initial data: 16 male and 16 female transsexual patients in Oregon
Crown Crisp Experiential Index (formerly Middlesex Hospital Questionnaire)	Developed circa 1966 Manual published 1970

Instrument Name and Developer	Development and Validation Information
<i>Crown & Crisp</i>	Initial data: 52 nursing students while in class in the UK
(2nd) European Quality of Life Survey <i>Anderson, Mikulić, Vermeylen, Lyly-Yrjanainen, & Zigante,</i>	Published in 2007 The pilot survey was tested in the UK and Holland with 200 interviews. The survey was revised especially for non-response questions. Another version was tested in 25 persons of each of the 31 countries to be surveyed. Sampling methods were devised. 35,634 Europeans were ultimately surveyed. Additional updates
Female Sexual Function Index <i>Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, Ferguson, D'Agostino Wiegel, Meston, & Rosen</i>	Published in 2000 Initial data: 131 normal controls & 128 age-matched subjects with female sexual arousal disorder from 5 U.S. research centers. Updated 2005: the addition of those with hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia/vaginismus, & multiple sexual dysfunctions (n=568), plus more controls (n=261).
Fragebogen zur Beurteilung des eigenen Körpers <i>Strauss</i>	Published 1996 (German)
Freiberg Personality Inventory <i>Fahrenberg, Hampel, & Selg</i>	7 th edition published 2001, 8 th edition in 2009 (Not in PubMed) German equivalent of MMPI
"gender identity disorder in childhood" <i>Smith, van Goozen, Kuiper, & Cohen-Kettenis</i>	11 items derived from the Biographical Questionnaire for Trans-sexuals (Verschoor Poortinga 1988) (Modified by authors of the Smith study)
Gender Identity Trait Scale <i>Altstotter-Gleich</i>	Published 1989 (German)
General Health Questionnaire <i>Goldberg & Blackwell (initial study)</i> <i>Goldberg & Williams (manual)</i>	Initial publication 1970 Manual published ?1978, 1988 (Not in PubMed) Initial data: 553 consecutive adult patients in a single UK primary care practice were assessed. Sample of 200 underwent standardized psychiatric interview. Developed to screen for hidden psychological morbidity. Proprietary test. Now 4 versions.
Hospital Anxiety & Depression Scale <i>Zigmond & Snaith</i>	Published in 1983 Initial data: Patients between 16 & 65 in outpatient clinics in the UK >100 patients; 2 refusals. 1 st 50 compared to 2 nd 50.
Inventory of Interpersonal Problems <i>Horowitz</i>	Published 1988 Initial data: 103 patients about to undergo psychotherapy; some patients post psychotherapy (Kaiser Permanente-San Francisco) Proprietary test
King's Health Questionnaire <i>Kelleher, Cardozo, Khullar, & Salvatore</i>	1997 Initial data: 293 consecutive women referred for urinary incontinence evaluation in London Comparison to SF-36
Minnesota Multi-phasic Personality Inventory <i>Hathaway & McKinley</i>	Published in 1941 Updated in 1989 with new, larger, more diverse sample.

Instrument Name and Developer	Development and Validation Information
<i>Butcher, Dahlstrom, Graham, & Tellegen</i>	MMPI-2: 1,138 men & 462 women from diverse communities & several geographic regions in the U.S.A. The test is copyrighted.
Modified Androphilia-Gyneophilia Index	Neither the underlying version or the Blanchard modified version could be located in PubMed (Designed by the author of the Blanchard et al. study)
"post-operative functioning 13 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
"post-operative functioning 21 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
Scale for Depersonalization Experiences <i>Wolfradt</i>	Unpublished manuscript 1998 (University of Halle) (Designed by 1 of the authors of the Wolfradt study)
"sex trait function" <i>Cohen-Kettenis & van Goozen</i>	Published 1997 Assessed in 22 adolescents (Designed by 1 of the authors of the Smith Study)
Self-Esteem Scale <i>Rosenberg</i>	Published 1965 (Not in PubMed) Initial data: 5,024 high-school juniors & seniors from 10 randomly selected New York schools
Short-Form 36 <i>RAND</i> <i>Ware & Sherbourne 1992</i> <i>McHorney, Ware, & Raczek 1993</i>	Originally derived from the Rand Medical Outcomes Study (n=2471 in version 1; 6742 in version 2 1989). The earliest test version is free. Alternative scoring has been developed. There is a commercial version with a manual.
Social Anxiety & Distress Scale <i>Watson & Friend</i>	Initial publication in 1969 Requires permission for use
Social Support Scale <i>Van Tilburg 1988</i>	Published 1988 (Dutch) (Not in PubMed)
Spielberger State & Trait Anxiety Questionnaire <i>Spielberger, Gorsuch, Lushene, Vagg, & Jacobs</i>	Current format published in 1983 Proprietary test
Symptom Checklist-90 <i>Derogatis, Lipman, Covi</i> <i>Derogatis & Cleary</i>	Published in 1973 & 1977 Reportedly with normative data for psychiatric patients (in- & out-patient) & normal subjects in the U.S. Has undergone a revision Requires qualification for use
Tennessee Self-Concept Scale <i>Fitts & Warren</i>	In use prior to 1988 publication. Initial data: 131 psychiatric day care patients. Updated manual published 1996. Update population >3000 with age stratification. No other information available. Requires qualification for use
Utrecht Gender Dysphoria Scale <i>Cohen-Kettenis & van Goozen</i>	Published in 1997 Initial population: 22 transgender adolescents who underwent reassignment surgery. (Designed by 1 of the authors of the Smith study)

Instrument Name and Developer	Development and Validation Information
WHO-Quality of Life (abbreviated version) <i>Harper for WHO group</i>	Field trial version released 1996 Tested in multiple countries. The Seattle site consisted of 192 of the 8294 subjects tested). Population not otherwise described. The minimal clinically important difference has not been determined. Permission required

Althof et al., 1983; Greenberg, Frank, 1965; Gurtman, 1996; Lang, Vernon, 1977; Paap et al., 2012; Salkind et al., 1969; Vacchiano, Strauss, 1968.

Appendix F

Endpoint Data Types and Sources

Panel A (Controlled Studies)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne 2011	Yes	-	-	-	-	Criminality, Mortality (Suicide, Cardiovascular Disease [possible adverse events from Hormone Tx], Cancer), Psych hx & hospitalization, Suicide attempts
Dhejne Landen	Yes	-	-	-	Includes demographics*	Criminality, Education, Employment, Formal application for reversal of status, Psych dx & tx, Substance abuse** More elements in earlier paper
Beatrice	-	MMPI form R, TSCS	-	-	Demographic	Education, Income, Relationships

Author	National Data	Instrument w/ Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Haraldsen	-	SCL-90/90R	-	-	Demographic	DSM Axis 1, II, V (GAF), Substance abuse
Heylens	-	SCL-90	-	Yes-2	Demographic	Employment, Relationships, Substance abuse, Suicide attempts
Ainsworth	-	Likely SF-36v2*	-	Yes-1	Demographic	-
Ruppin	-	SCL-90R	BSRI, FPI-R, IIP	Yes-2	Demographic	Adverse events from surgery, Employment, Psych tx, Relationships, Substance abuse
Smith	-	MMPI-short, SCL-90?R	BIS, UGDS, ? Cohen-Kettenis', Doorn's x2, (Gid-c, SSS)	Yes-1 or 2	Demographic	Adverse events from surgery, Employment, Relationships
Udeze Megeri	-	SCL-90R	BDI, GHQ, HADS, STAI-X1, STAI-X2	-	-	Psych eval & ICD-10 dx
Kuhn	-	-	KHQ	Yes-1	Demographic	Relationships
Mate-Kole 1990	-	-	BSRI, CCEI	Yes-1	Demographic	Employment (relative change), Psych hx, Suicide hx
Wolfradt	-	-	BIQ, GITS, SDE, SES	Yes-1	-	-
Kraemer	-	-	FBeK	-	Demographic	-
Mate-Kole 1988	-	-	BSRI, CCEI	-	Demographic	Employment, Psych hx, Suicide hx,
Kockott	-	-	-	Yes-1	Demographic	Employment, Income, Relationships, Suicide attempts
Meyer	-	-	-	Yes-1	Demographic	Education, Employment, Income, Psych tx, Phallus removal request
Rakic	-	-	-	Yes-1	Demographic	Employment, Relationships

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Weyers	-	SF-36	FSFI	Yes-2	Demographic	Hormone levels, Adverse events from surgery, Relationships
Blanchard	-	SCL-90R	(AG)	Yes-1	Demographic	Education, Employment, Income, Relationships, Suicide (Incidental finding)
Wierckx	-	SF-36	-	Yes-3	Demographic	Hormone levels, Adverse events from surgery, Relationships
Eldh	-	-	-	Yes-1	-	Adverse events from surgery, Employment, Relationships, Suicide attempts
Hess	-	-	-	Yes-1	-	-
Lawrence	-	-	-	Yes-4	Demographic	Adverse events from surgery
Salvador	-	-	-	Yes-1	Demographic	Relationships
Tsoi	-	-	-	Yes-1	Demographic	Education, Employment, Relationships (relative change)

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Asscherman et al.	Yes	-	-	-	Demographic	

Author	National Data	Instrument w/ Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
						Mortality (HIV, Possible adverse events from Hormone Tx, Substance abuse, Suicide)
Motmans et al.	-	SF36 EQOLS (2 nd)	-	-	Demographic	Education, Employment, Income, Relationships
Newfield et al.	-	SF-36v2	-	-	Demographic	Income
Gómez-Gil et al. 2014	-	WHOQOL-BREF	APGAR	Yes-1	Demographic	Education, Employment, Relationships
Gómez-Gil et al. 2012	-	-	HADS, SADS	-	Demographic	Education, Employment, Living arrangements
Hepp et al.	-	-	HADS	-	Demographic	DSM Axis 1& II Psych dx
Johansson et al.	-	-	-	Yes-1	Demographic	Axis V change (Pt & Clinician) Employment (relative change) Relationship (relative change)
Leinung et al.	-	-	-	-	Demographic	Employment, Disability, DVT, HIV status, Psych dx

*Listed as San Francisco-36 in manuscript

** From medical charts & verdicts ?=Possibly self-designed

AG=Androphilia-Gynephilia Index (investigator designed 1985) (used more for classification)

APGAR=Family Adaptability, Partnership growth, Affection, and Resolve

BDI=Beck Depression Inventory

BIQ=Body Image Questionnaire

BIS=Body Image Scale

BSRI=Bem Sex Role Inventory

CCEI=Crown Crisp Experiential Index

Cohen-Kettenis'= Sex trait function (An author helped design)

Dorn's x2= Post-operative functioning 13 items (An author helped design)

Post-operative functioning 21 items (An author helped design)

EQOLS (2nd)=2nd European Quality of Life Survey

FBeK=Fragebogen zur Beurteilung des eigenen Körpers

FPI-R=A version of the Freiberg Personality Inventory

FSFI+Female Sexual Function Index

GHQ=General Health Questionnaire

Gid-c=Gender identity disorder in childhood (used more for predictors) (An author helped design)

GITS=Gender Identity Trait Scale

HADS=Hospital Anxiety Depression Scale

MMPI=Minnesota Multi-phasic Personality Inventory

SADS=Social Anxiety & Distress Scale

SCL-90 (±R)=A version of the Symptom Checklist 90

SDE=Scale for Depersonalized Experiences (An author designed)

SES=Self-Esteem Scale

SF-36 (v2)=Short Form-36(version2)

SSS=Social Support Scale (used more for predictors)

STAI-X1, STAI-X2=Spielberger State and Trait Anxiety Questionnaire

TSCS=Tennessee Self-Concept Scale

UGDS=Utrecht Gender Dysphoria Scale (An author helped design)

WHOQOL-BREF=World Health Organization-Quality of Life (abbreviated version)

Appendix G.**Longitudinal Studies Which Used Patients as Their Own Controls and Which Used Psychometric Tests with Extensive Normative Data or Longitudinal Studies Which Used National Data Sets**

Author	Test	Patient and Data Loss	Results
Psychometric Test			
Heylens et al. Belgium 2014	SCL-90R	<p>90 applicants for SRS were recruited.</p> <ul style="list-style-type: none"> •8 (8.9%) declined participation. •12 (13.3%) excluded b/c GID-NOS dx. •12 (13.3%) did not complete the treatment sequence b/c of psychiatric/physical comorbidity, personal decision for no tx, or personal decision for only hormone tx. •1 (1.1%) committed suicide during follow-up. <p>57 (63.3% of recruited) entered the study.</p> <ul style="list-style-type: none"> •1 (12.2% of initial recruits) had not yet received SRS by study close. <p>46 (51.1% of recruited) underwent serial evaluation</p> <ul style="list-style-type: none"> •The test was not completed by 1 at t=0, 10 at t=1 (after hormone tx), & 4 at t=2 (after SRS) <p>missing data for another 1.1% to 11.1%.</p>	<p>At t=0, the mean global "psychoneuroticism" SCL-90R score, along with scores of 7 of 8 subscales, were statistically more pathologic than the general population.</p> <p>After hormone tx, the mean score for global "psychoneuroticism" normalized & remained normal after reassignment surgery.</p>
Ruppin,Pfafflin, Germany 2015	SCL-90R	The number in the available patient pool was not specified.	

Author	Test	Patient and Data Loss	Results
		<p>140 received recruitment letters.</p> <ul style="list-style-type: none"> •2 (1.4% of those with recruitment letters) had died. •1 (0.7%) was institutionalized. •5 (3.6%) were ill. •8 (5.7%) did not have time. •8 (5.7%) stated that GD was no longer an issue. •8 (5.7%) provided no reason. •28 (20.0%) declined further contact. •9 (6.4%) were lost to follow-up. <p>71 (50.7%) agreed to participate.</p> <p>•2 (1.4%) had not undergone SRS</p> <p>•The test was not completed by 9.</p> <p>missing data for another 6.4%.</p>	<p>At t=0, the "global severity index "SCL-90R score was 0.53 ± 0.49. At post-SRS follow-up the score had decreased to 0.28 ± 0.36.</p> <p>The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 0-4.</p> <p>In the same way, all of the subscale scores were statistically different, but the effect size was reported as large only for "interpersonal sensitivity": 0.70 ± 0.67 at t=0 and 0.26 ± 0.34 post-SRS.</p>
Smith et al. Holland 2005	MMPI SCL-90	<p>The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited.</p> <ul style="list-style-type: none"> •103 (31.7%) were not eligible to start hormone tx & real-life experience. •34 (10.7%) discontinued hormone tx <p>162 (an unknown percentage of the initial recruitment) provided pre-SRS test data.</p> <p>•36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete post-SRS testing.</p>	<p>Most of the MMPI scales were already in the normal range at the time of initial testing.</p> <p>At t=0, the global "psychoneuroticism" SCL-90 score, which included the drop-outs, was 143.0 ± 40.7.</p> <p>At post SRS-follow-up, the score had decreased to 120.3 ± 31.4.</p> <p>The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 90 to 450, with higher scores consistent with more psychological instability.</p>
Udeze, et al. 2008 Megeri, Khoosal 2007 UK	SCL-90R	<p>The number in the available patient pool was not specified. 40 subjects were prospectively selected.</p> <ul style="list-style-type: none"> •Post-operative testing was conducted within 6 months to minimize previously determined loss rates. 	<p>At t=0, the mean raw global score was 48.33. At post-SRS follow-up, the mean score was 49.15.</p>

Author	Test	Patient and Data Loss	Results
			There were no statistically significant changes in the global score or for any of the subscales.
National Databases			
Dehjne Sweden 2011	Swedish National Records	<p>804 with GID in Sweden 1973 to 2003 were identified.</p> <ul style="list-style-type: none"> •480 (59.7%) did not apply or were not approved for SRS 324 (40.3%) underwent SRS. •All were followed. <p>3240 controls of the natal sex and 3240 controls of the reassigned gender were randomly selected from national records</p>	<p>All cause mortality was higher (n=27[8%]) than in controls (H.R. 2.8 [1.8-4.3]) even after adjustment for covariants. Divergence in survival curves was observed after 10 years. The major contributor was completed suicide (n=10 [3%]; adjusted H.R. 19.1 [5.8-62.9]).</p> <p>Suicide attempts were more common (n= 29 [9%]) than in controls (adjusted H.R. 4.9 [2.9-8.5]).</p> <p>Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common n= 64 [20%] than in controls (H.R. 2.8 [2.0-3.9]) even after adjusting for prior psychiatric morbidity.</p>
Dhejne et al. 2014 Landen et al. 1998 Sweden	Swedish National Registry	<p>767 applied for SRS/legal status (1960-2010)</p> <ul style="list-style-type: none"> •25 (3.3%) applications denied. •61 (8.0%) not granted full legal status <p>681 (88.7%) underwent SRS.</p> <ul style="list-style-type: none"> •All were followed. 	<p>15 formal applications for reversal to natal/original gender (2.2% of the SRS population) were identified thus far (preliminary number). (Does not reflect other manifestations of regret such as suicide.)</p>

GID=NOS=Gender Identity Disorder-Not Otherwise Specified HR=Hazard Ratio SRS=Sex reassignment surgery
Tx=Treatment [Back to Top](#)

Bibliography

ACA 2010: Patient Protection and Affordable Care Act, Pub. L. No. 111 -148, §3502, 124 Stat. 119, 124 (2010).

Ahmed SF, Morrison S, Hughes IA. Intersex and gender assignment; the third way? *Arch Dis Child*. 2004 Sep;89(9):847-50. PMID: 15321864.

Ainsworth T, Spiegel J. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. *Qual Life Res.* 2010 Sep;19(7):1019-24. Epub 2010 May 12. PMID: 20461468.

Altstotter-Gleich, C. (1989). *Theoriegeleitete Itemkonstruktion und -auswahl: Eine Modifikation des Einsatzes der Repertory-Grid-Technik dargestellt am Beispiel der Erfassung der Geschlechtsidentität* [Theory oriented item construction and selection: A modification of the use of the Repertory-Grid-Technique as shown at the example of the assessment of gender identity], Verlag für empirische Pädagogik, Landau. German. (Not in PubMed)

Althof SE, Lothstein LM, Jones P, Shen J. An MMPI subscale (Gd): to identify males with gender identity conflicts. *J Pers Assess.* 1983 Feb;47(1):42-9. PMID: 6834232.

American College of Obstetricians and Gynecologists (ACOG). Committee on Health Care for Underserved Women. Committee Opinion No. 512: Health care for transgender individuals. *Obstet Gynecol.* 2011 Dec;118(6):1454-8.

American Medical Association House of Delegates resolution 122 (A-08) proposal *Removing Financial Barriers to Care for Transgender Patients.* 2008.

American Psychological Association (APA). Guidelines for Psychological Practice with Transgender and Gender Nonconforming People. *American Psychologist*: 2015: Adopted by the Council of Representatives, August 5 & 7, 2015. www.apa.org/practice/guidelines/transgender.pdf (publication pending).

Antoszewski B, Bratoś R, Sitek A, Fijałkowska M. Long-term results of breast reduction in female-to-male transsexuals. *Pol Przegl Chir.* 2012 Mar;84(3):144-51. PMID: 22659357.

Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-Aranda F. Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur Psychiatry.* 2015 Sep;30(6):807-15. Epub 2015 May 26. PMID: 26021270.

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011 Apr;164(4):635-42. Epub 2011 Jan 25. PMID: 21266549.

Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola M, Mueller A, Kuhn A, Dhejne C, Morel-Journel N, Gooren L. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia*. 2014 Sep;46(7):791-5. Epub 2013 Aug 15. PMID: 23944849.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 June;328(19):1490-4. PMID: 15205295.

Auer M, Fuss J, Stalla G, Athanasoulia A. Twenty years of endocrinologic treatment in transsexualism: analyzing the role of chromosomal analysis and hormonal profiling in the diagnostic work-up. *Fertil Steril* 2013 Oct;100(4):1103-10. Epub 2013 Jun 27.

Auerbach JD. The iPrEx results: lifting hopes, raising questions. *BETA*. 2010 Summer-Fall;22(4):47-9. PMID: 21591604.

Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T. Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *J Sex Med*. 2011 Jun;8(6):1686-93. Epub 2011 Apr 7. PMID: 21477021.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011 Apr;64(4):401-6. Epub 2011 Jan 5. PMID: 21208779.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. *J Nerv Ment Dis.* 1985 Jun;173(6):358-65. PMID: 3998721.

Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* .1961 Jun;4:561-71. PMID: 13688369.

Bentz EK, Hepler LA, Kaufmann U, Huber JC, Kolbus A, Tempfer CB. A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to-female transsexualism. *Fertil Steril.* 2008 Jul;90(1):56-9. Epub 2007 Sep 4. PMID: 17765230.

Bentz EK, Pils D, Bilban M, Kaufmann U, Hepler LA, Reinthaller A, Singer CF, Huber JC, Horvat R, Tempfer CB. Gene expression signatures of breast tissue before and after cross-sex hormone therapy in female-to-male transsexuals. *Fertil Steril.* 2010 Dec;94(7):2688-96. Epub 2010 May 26. PMID: 20537635.

Bem, S. L. (1974). The measurement of psychological androgyny. *Journal of Consulting and Clinical Psychology.* 1974; 42:155-162. (Not in PubMed)

Berry MG, Curtis R, Davies D. Female-to-male transgender chest reconstruction: a large consecutive, single-surgeon experience. *J Plast Reconstr Aesthet Surg.* 2012 Jun;65(6):711-9. Epub 2011 Dec 19. PMID: 22189204.

Besnier, N. (1994). Polynesian gender liminality through time and space. In G.Herdt (Ed.), *Third sex, third gender: Beyond sexual dimorphism in culture and history.* New York: Zone Books.

Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol.* 1988 Sep;61 (Pt 3):255-66. PMID: 3179248.

Bjerrome Ahlin H, Kölby L, Elander A, Selvaggi G. Improved results after implementation of the Ghent algorithm for subcutaneous mastectomy in female-to-male transsexuals. *J Plast Surg Hand Surg*. 2014 Dec;48(6):362-7. Epub 2014 Mar 11. PMID: 24611803.

A-Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304. PMID: 4008715.

B-Blanchard R. Typology of male-to-female transsexualism. *Arch Sex Behav*. 1985 Jun;14(3):247-61. PMID: 4004548.

C-Blanchard RJ, Blanchard DC, Flannelly KJ. Social desirability response set and systematic distortion in the self-report of adult male gender patients. *Behav Processes*. 1985 Aug;11(2):209-13. doi: 10.1016/0376-6357(85)90062-2. PMID: 24895927.

D-Blanchard, R. (1985). *Research methods for the typological study of gender disorders in males*. In B. W. Steiner (Ed.), *Gender dysphoria: Development, research, management* (pp. 227-257). New York: Plenum Press.

Blanchard R, Clemmensen LH, Steiner BW. Heterosexual and homosexual gender dysphoria. *Arch Sex Behav*. 1987 Apr;16(2):139-52. PMID: 3592961.

Blanchard R, Steiner BW, Clemmensen LH, Dickey R. Prediction of regrets in postoperative transsexuals. *Can J Psychiatry*. 1989 Feb;34(1):43-5. PMID: 2924248.

Bockting W, Coleman E, De Cuypere G. Care of transsexual persons. *N Engl J Med*. 2011 Jun 30;364(26):2559-60; author reply 2560. PMID: 21714669.

Bodlund O, Armelius K. Self-image and personality traits in gender identity disorders: an empirical study. *J Sex Marital Ther.* 1994 Winter;20(4):303-17. PMID: 7897678.

Bodlund O, Kullgren G. Transsexualism general outcome and prognostic factors: a five-year follow-up study of nineteen transsexuals in the process of changing sex. *Arch Sex Behav.* 1996 Jun;25(3):303-16. PMID: 8726553.

Boehmer AL, Brinkmann AO, Sandkuijl LA, Halley DJ, Niermeijer MF, Andersson S, de Jong FH, Kayserili H, de Vroede MA, Otten BJ, Rouwé CW, Mendonça BB, Rodrigues C, Bode HH, de Ruiter PE, Delemarre-van de Waal HA, Drop SL. 17Beta-hydroxysteroid dehydrogenase-3 deficiency: diagnosis, phenotypic variability, population genetics, and worldwide distribution of ancient and de novo mutations. *J Clin Endocrinol Metab.* 1999 Dec;84(12):4713-21. PMID: 10599740.

Boehmer U. Twenty years of public health research: inclusion of lesbian, gay, bisexual, and transgender populations. *Am J Public Health.* 2002 Jul;92(7):1125-30. PMID: 12084696.

Bonifacio HJ, Rosenthal SM. Gender Variance and Dysphoria in Children and Adolescents. *Pediatr Clin North Am.* 2015 Aug;62(4):1001-16. Epub 2015 Jun 11. PMID: 26210629.

Borsboom D, Mellenbergh GJ, van Heerden J. The theoretical status of latent variables. *Psychol Rev.* 2003 Apr;110(2):203-19. PMID: 12747522.

Bouman M, van Zeijl M, Buncamper M, Meijerink W, van Bodegraven A, Mullender M. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. *J Sex Med.* 2014 Jul;11(7):1835-47. Epub 2014 Apr 4. PMID: 24697986.

Bowman E, Oprea G, Okoli J, Gundry K, Rizzo M, Gabram-Mendola S, Manne U, Smith G, Pambuccian S, Bumpers HL. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. *Breast J.* 2012 May-Jun;18(3):242-7. PMID: 22583194.

Brown L (Ed.). (1997) *Two Spirit People: American Indian, lesbian women and gay men*. Routledge.

Bye L, Gruskin E, Greenwood, G, Albright V, Krotki K. California Lesbians, Gays, Bisexuals, and Transgender (LGBT) Tobacco Use Survey – 2004. *Sacramento, CA: California Department of Health Services*, 2005. (Not in PubMed)

Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. American Psychiatric Association. Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav* 2012 Aug;41(4):759-96. PMID: 22854940.

Callens N, De Cuypere G, Van Hoecke E, T'sjoen G, Monstrey S, Cools M, Hoebeke P. Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis: a review. *J Sex Med*. 2013 Dec;10(12):2890-903. Epub 2013 Aug 23. PMID: 23981815.

Callens N, Hoebeke P. Phalloplasty: A panacea for 46, XY disorder of sex development conditions with penile deficiency? *Endocr Dev*. 2014;27:222-33. Epub 2014 Sep 9. PMID: 25247659.

Cameron D. Language, gender, and sexuality: Current issues and new directions. *Applied Linguistics*. 2005; 26(4):482-502. (Not in PubMed)

Casella R, Bubendorf L, Schaefer D, Bachmann A, Gasser T, Sulser T. Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int*. 2005;75(3):288-90. PMID: 16215322.

Cantor JM. New MRI studies support the Blanchard typology of male-to-female transsexualism. *Arch Sex Behav*. 2011 Oct;40(5):863-4. PMID: 21739338.

Cebula H, Pham TQ, Boyer P, Froelich S. Regression of meningiomas after discontinuation of cyproterone acetate in a transsexual patient. *Acta Neurochir (Wien)*. 2010 Nov;152(11):1955-6. Epub 2010 Sep 3. PMID: 20811919.

Cerwenka S, Nieder T, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Kreukels B, Richter-Appelt H. Sexual behavior of gender-dysphoric individuals before gender-confirming interventions: a European multicenter study. *J Sex Marital Ther* 2014;40(5):457-71. PMID: 24846436.

Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet*. 2005 Mar 26-Apr 1;365(9465):1159-62. PMID: 15794971.

Chen S, McFarland W, Thompson HM, Raymond HF. Transmen in San Francisco: what do we know from HIV test site data? *AIDS Behav*. 2011 Apr;15(3):659-62. PMID: 21153048.

Chinas, B. (1995). Isthmus Zapotec attitudes toward sex and gender anomalies. In S. O. Murray (Ed.), *Latin American male homosexualities* (pp. 293-302). Albuquerque, NM: University of New Mexico Press.

Chiong W. The real problem with equipoise. *Am J Bioeth*. 2006 Jul-Aug;6(4):37-47. PMID: 16885104.

CHIS 2009: California Health Interview Survey, 2009. "AskCHIS" via the UCLA Center for Health Policy Research date website ask.chis.ucla.edu/.

Chong JM. Social assessment of transsexuals who apply for sex reassignment therapy. *Soc Work Health Care*. 1990;14(3):87-105. PMID: 2367927.

Claes L, Bouman W, Witcomb G, Thurston M, Fernandez-Aranda F, Arcelus J. Non-suicidal self-injury in trans people: associations with psychological symptoms, victimization, interpersonal functioning, and perceived social support. *J Sex Med*. 2015 Jan;12(1):168-79. Epub 2014 Oct 6. PMID: 25283073.

Clement U, Löwe B. [Validation of the FKB-20 as scale for the detection of body image distortions in psychosomatic patients]. *Psychother Psychosom Med Psychol*. 1996 Jul;46(7):254-9. German. PMID: 8765897.

Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *J Homosex*. 2006;51(3):53-69. PMID: 17135115.

Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997 Feb;36(2):263-71. PMID: 9031580.

A Cohen-Kettenis P. Psychological long-term outcome in intersex conditions. *Horm Res*. 2005;64 Suppl 2:27-30. PMID: 16286767.

B Cohen-Kettenis PT. Gender change in 46 XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005 Aug;34(4):399-410. PMID: 16010463.

Cohen-Kettenis P, Pfäfflin F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Arch Sex Behav*. 2010 Apr;39(2):499-513. PMID: 19838784.

Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress in gender identity disorder, independently of the attachment style. *J Sex Med*. 2013 Dec;10(12):3049-58. Epub 2013 Apr 9. PMID: 23574768.

Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology*. 2014 Jan;39:65-73. Epub 2013 Oct 10. PMID: 24275005.

Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, Quagliarella L, Brescia F, Natilla LC, Loverro G, Todarello O. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *J Psychosom Res*. 2015 Apr;78(4):399-406. Epub 2014 Feb 10. PMID: 25416810.

Coleman E, Colgan P, Gooren L. Male cross-gender behavior in Myanmar (Burma): A description of the acault. *Arch Sex Behav.* 1992 Jun;21(3):313-21. PMID: 1535191.

Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R, Wylie KR, Zucker K. World Professional Association for Transgender Health (formerly the Harry Benjamin International Gender Dysphoria Association). Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People (Version 7). *Int J Transgend.* 2011;13:165–232. © 2012 World Professional Association for Transgender Health (WPATH). (not in Pubmed) www.wpath.org/uploaded_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf.

Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from a household probability sample of adults. *Am J Public Health.* 2012 Jan;102(1):118-22. Epub 2011 Nov 28. PMID: 22095354.

Corsello SM, Di Donna V, Senes P, Luotto V, Ricciato MP, Paragliola RM, Pontecorvi A. Biological aspects of gender disorders. *Minerva Endocrinol.* 2011 Dec;36(4):325-39. PMID: 22322655.

Costa L M, Matzner A. (2007). *Male bodies, women’s souls: Personal narrative of Thailand’s transgendered youth.* Routledge.

Costantino A, Cerpolini S, Alvisi S, Morselli P, Venturoli S, Meriggiola M. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther.* 2013;39(4):321-35. Epub 2013 Mar 7. PMID: 23470169.

Cregten-Escobar P, Bouman M, Buncamper M, Mullender M. Subcutaneous mastectomy in female-to-male transsexuals: a retrospective cohort-analysis of 202 patients. *J Sex Med* 2012 Dec;9(12):3148-53. PMID: 23470169.

Crown S, Duncan KP, Howell RW. Further evaluation of the Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry*. 1970 Jan;116(530):33-7. PMID: 5411005.

Crown S. The Middlesex Hospital Questionnaire (MHQ) in clinical research. A review. *Mod Probl Pharmacopsychiatry*. 1974;7(0):111-24. PMID: 4607280.

Cupisti S, Giltay EJ, Gooren LJ, Kronawitter D, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril*. 2010 Dec;94(7):2647-53. Epub 2010 May 7. PMID: 20451188.

Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Vansteenwegen A, Rubens R. Sexual and physical health after sex reassignment surgery. *Arch Sex Behav*. 2005 Dec;34(6):679-90. PMID: 16362252.

De Cuypere G, Elaut E, Heylens G, van Maele G, Selvaggi G, T'Sjoen G, Rubens R, Hoebeke R, Monstrey S. Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. *J Sexol*. 2006;15:126-33. (Not in PubMed)

De Cuypere G, Van Hemelrijck M, Michel A, Carael B, Heylens G, Rubens R, Hoebeke P, Monstrey S. Prevalence and demography of transsexualism in Belgium. *Eur Psychiatry*. 2007 Apr;22(3):137-41. Epub 2006 Dec 26. PMID: 17188846.

Deipolyi AR, Han SJ, Parsa AT. Development of a symptomatic intracranial meningioma in a male-to-female transsexual after initiation of hormone therapy. *J Clin Neurosci*. 2010 Oct;17(10):1324-6. Epub 2010 Jul 1. PMID: 20594855.

Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale preliminary report. *Psychopharmacol Bull*. 1973 Jan;9(1):13-28. PMID: 4682398.

A-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci*. 1974 Jan;19(1):1-15. PMID:

B-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL). A measure of primary symptom dimensions. *Mod Probl Pharmacopsychiatry*. 1974;7(0):79-110. PMID: 4607278.

Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. *Br J Soc Clin Psychol*. 1977 Nov;16(4):347-56 PMID: 588890.

Derogatis LR, Meyer JK, Vazquez N. A psychological profile of the transsexual. I. The male. *J Nerv Ment Dis*. 1978 Apr;166(4):234-54. PMID: 650186.

Deutsch M, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. *Obstet Gyneco*. 2015 Mar;125(3):605-10. PMID: 25730222.

de Vries A, Kreukels B, Steensma T, Doreleijers T, Cohen-Kettenis P. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res* 2011 Apr 30;186(2-3):414-8. PMID: 20801524.

Case 1:16-cv-00108-0 Document 26 Filed 10/25/16 Page 589 of 919 Page 158 of 155
Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: a cohort study. *J Sex Med.* 2011 Feb;6(2):158-65. Epub 2011 Feb 22. PMID: 21364939.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Arch Sex Behav.* 2014 Nov;43(8):1535-45. Epub 2014 May 29. PMID: 24872188.

Dhillon R, Bastiampillai T, Krishnan S, Opray N, Tibrewal P. Transgender late onset psychosis: the role of sex hormones. *Aust N Z J Psychiatry.* 2011 Jul;45(7):603. Epub 2011 May 5. PMID: 21542781.

Diamond M. Developmental, sexual and reproductive neuroendocrinology: historical, clinical and ethical considerations. *Front Neuroendocrinol.* 2011 Apr;32(2):255-63. Epub 2011 Feb 18. PMID: 21310174.

Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann M, Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes.* 2005 Dec;113(10):586-92. PMID: 16320157.

Djordjevic ML, Stanojevic DS, Bizic MR. Rectosigmoid vaginoplasty: clinical experience and outcomes in 86 cases. *J Sex Med.* 2011 Dec;8(12):3487-94. Epub 2011 Oct 13. PMID: 21995738.

Djordjevic ML, Bizic MR. Comparison of two different methods for urethral lengthening in female to male (metoidioplasty) surgery. *J Sex Med.* 2013 May;10(5):1431-8. Epub 2013 Feb 27. PMID: 23444841.

Doorduyn T, van Berlo W. Trans people's experience of sexuality in the Netherlands: a pilot study. *J Homosex.* 2014;61(5):654-72. PMID: 24295055.

Doorn CD, Poortinga J, Verschoor AM. Cross-gender identity in transvestites and male transsexuals. *Arch Sex Behav.* 1994 Apr;23(2):185-201. PMID: 8018022.

Doornaert M, Hoebeke P, Ceulemans P, T'Sjoen G, Heylens G, Monstrey S. Penile reconstruction with the radial forearm flap: an update. *Handchir Mikrochir Plast Chir*. 2011 Aug;43(4):208-14. Epub 2011 Aug 11.

A-Dos Ramos Farías MS, Picconi MA, Garcia MN, González JV, Basiletti J, Pando Mde L, Avila MM. Human papilloma virus genotype diversity of anal infection among trans (male to female transvestites, transsexuals or transgender) sex workers in Argentina. *J Clin Virol*. 2011 Jun;51(2):96-9. Epub 2011 Apr 20. PMID: 21511521.

B-Dos Ramos Farías MS, Garcia MN, Reynaga E, Romero M, Vaulet ML, Fermepín MR, Toscano MF, Rey J, Marone R, Squiquera L, González JV, Basiletti J, Picconi MA, Pando MA, Avila MM. First report on sexually transmitted infections among trans (male to female transvestites, transsexuals, or transgender) and male sex workers in Argentina: high HIV, HPV, HBV, and syphilis prevalence. *Int J Infect Dis*. 2011 Sep;15(9):e635-40. Epub 2011 Jul 13. PMID: 21742530.

DSM: American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, D.C: American Psychiatric Association.

Dubois L. Associations between transition-specific stress experience, nocturnal decline in ambulatory blood pressure, and C-reactive protein levels among transgender men. *Am J Hum Biol* 2012 Jan-Feb;24(1):52-61. Epub 2011 Nov 28. PMID: 22120883.

Duisin D, Nikolić-Balkoski G, Batinić B. Sociodemographic profile of transsexual patients. *Psychiatr Danub*. 2009 Jun;21(2):220-3. PMID: 19556952.

Duišin D, Batinić B, Barišić J, Djordjevic ML, Vujović S, Bizic M. Personality disorders in persons with gender identity disorder. *ScientificWorldJournal*. 2014;2014:809058. Epub 2014 May 13. PMID: 24959629.

Dunn, OJ. Multiple Comparisons Among Means. *J Am Statis Assoc*. 1961 Mar; 56(293): 52- 64. (Not in PubMed) www.jstor.org/stable/2282330.

Elamin M, Garcia M, Murad M, Erwin P, Montori V. Effect of sex steroid use on cardiovascular risk in transsexual individuals. *Case Reports Endocrinol Metab*. 2016 Jun;1(1):1-6. Epub 2016 Jun 22. PMID: 2711174. Case 7:16-cv-00108-D Document 26 Filed 10/21/16 Page 691 of 919 PageID 115

Elaut E, Bogaert V, De Cuypere G, Weyers S, Gijs L, Kaufman J, T'Sjoen G. Contribution of androgen receptor sensitivity to the relation between testosterone and sexual desire: An exploration in male-to-female transsexuals. *J Endocrinol Invest*. 2010 Jan;33(1):37-41. Epub 2009 Jul 20. PMID: 19620824.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. *Scand J Plast Reconstr Surg Hand Surg*. 1997 Mar;31(1):39-45. PMID: 9075286.

Ettner R. Care of the elderly transgender patient. *Curr Opin Endocrinol Diabetes Obes* 2013 Dec;20(6):580-4. PMID: 24468762.

Europe QOL 2010 Anderson R, Mikulić B, Vermeylen G, Lyly-Yrjanainen M, Zigante V. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work -Overview*. EF0902. December 13, 2010. www.eurofound.europa.eu/publications/report/2009/quality-of-life/second-european-quality-of-life-survey-overview.

Europe QOL 2011 Kotowska IE, Matysiak A, Styrac M, Pailhe A, Solaz, A Vignoli D. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work*. EF1002. August 22, 2011. NLM classification: WC 503.6. www.eurofound.europa.eu/publications/report/2010/quality-of-life-social-policies/second-european-quality-of-life-survey-family-life-and-work.

Fares WH. The 'availability' bias: underappreciated but with major potential implications. *Crit Care*. 2014 Mar 12;18(2):118. PMID: 25029621.

Ferring D, Filipp SH. Messung des Selbstwertgefühls: Befunde zu Reliabilität, Validität und Stabilität der Rosenberg-Skala [Measurement of self-esteem: Findings on reliability, validity, and stability of the Rosenberg Scale]. *Diagnostica*. 1996; 42: 284-292. German. (Not in PubMed)

Fisher AD, Bandini E, Casale H, Ferruccio N, Meriggiola MC, Gualerzi A, Manieri C, Jannini E, Mannucci E, Monami M, Stomaci N, Delle Rose A, Susini T, Ricca V, Maggi M. Sociodemographic and clinical features of gender identity disorder: an Italian multicentric evaluation. *J Sex Med*. 2013 Feb;10(2):408-19. Epub 2012 Nov 21. PMID: 23171237.

Flanagan BM, Philpott S, Strosberg MA. Protecting participants of clinical trials conducted in the intensive care unit. *J Intensive Care Med*. 2011 Jul-Aug;26(4):237-49. PMID: 21764767.

Fleming M, Steinman C, Bocknek G. Methodological problems in assessing sex-reassignment surgery: a reply to Meyer and Reter. *Arch Sex Behav*. 1980 Oct;9(5):451-6. PMID: 7447685.

Fleming M, Cohen D, Salt P, Jones D, Jenkins S. A study of pre- and postsurgical transsexuals: MMPI characteristics. *Arch Sex Behav*. 1981 Apr;10(2):161-70. PMID: 7247725.

Frances AJ, Nardo JM. ICD-11 should not repeat the mistakes made by DSM-5. *Br J Psychiatry*. 2013 Jul;203(1):1-2. PMID: 23818530.

Frade-Costa EM, Bilharinho Mendonca B. Clinical management of transsexual subjects. *Arq Bras Endocrinol Metab*. 2014;58(2):188-96. (Not in PubMed)

Franco T, Miranda L, Franco D, Zaidhaft S, Aran M. Male-to-female transsexual surgery: experience at the UFRJ University Hospital. *Rev Col Bras Cir*. 2010 Dec;37(6):426-34. PMID: 21340258.

Fuss J, Biedermann S, Stalla G, Auer M. On the quest for a biomechanism of transsexualism: is there a role for BDNF? *J Psychiatr Res*. 2013 Dec;47(12):2015-7. Epub 2013 Sep 7. PMID: 23915300.

Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav*. 1998 Apr;27(2):209-26. PMID: 9562902.

Garaffa G, Raheem AA, Ralph DJ. An update on penile reconstruction. *Asian J Androl*. 2011 May;13(3):391-4. PMID: 22426595.

Garaffa G, Gentile V, Antonini G, Tsafrakidis P, Raheem AA, Ralph DJ. Penile reconstruction in the male. *Arab J Urol*. 2013 Sep;11(3):267-71. Epub 2013 Jun 12. PMID: 26558091.

Garcia-Falgueras A, Swaab DF. Sexual hormones and the brain: an essential alliance for sexual identity and sexual orientation. *Endocr Dev*. 2010;17:22-35. Epub 2009 Nov 24. PMID: 19955753.

Garcia-Falgueras A, Ligtenberg L, Kruijver FP, Swaab DF. Galanin neurons in the intermediate nucleus (InM) of the human hypothalamus in relation to sex, age, and gender identity. *J Comp Neurol*. 2011 Oct 15;519(15):3061-84. PMID: 21618223.

García-Malpartida K, Martín-Gorgojo A, Rocha M, Gómez-Balaguer M, Hernández-Mijares A. Prolactinoma induced by estrogen and cyproterone acetate in a male-to-female transsexual. *Fertil Steril*. 2010 Aug;94(3):1097.e13-5. Epub 2010 Mar 12. PMID: 20227072.

Garrels L, Kockott G, Michael N, Preuss W, Renter K, Schmidt G, Sigusch V, Windgassen K. Sex ratio of transsexuals in Germany: the development over three decades. *Acta Psychiatr Scand*. 2000 Dec;102(6):445-8. PMID: 11142434.

Gaspari L, Paris F, Philibert P, Audran F, Orsini M, Servant N, Maïmoun L, Kalfa N, Sultan C. 'Idiopathic' partial androgen insensitivity syndrome in 28 newborn and infant males: impact of prenatal exposure to environmental endocrine disruptor chemicals? *Eur J Endocrinol*. 2011 Oct;165(4):579-87. Epub 2011 Jul 25. PMID: 21788424.

Giami A, Le Bail J. HIV infection and STI in the trans population: a critical review. *Rev Epidemiol Sante Publique*. 2011 Aug;59(4):259-68. Epub 2011 Jul 20. PMID: 21767925.

Glezer A, McNeil D, Binder R. Transgendered and incarcerated: a review of the literature, current policies and laws, and ethics. *J Am Acad Psychiatry Law*. 2013;41(4):551-9. PMID: 24335329.

A-Goddard JC, Vickery RM, Terry TR. Development of feminizing genitoplasty for gender dysphoria. *J Sex Med*. 2007 Jul;4(4 Pt 1):981-9. Epub 2007 Apr 19. PMID: 17451484.

B-Goddard JC, Vickery RM, Qureshi A, Summerton DJ, Khoosal D, Terry TR. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. *BJU Int*. 2007 Sep;100(3):607-13. PMID: 17669144.

Godlewski J. Transsexualism and anatomic sex ratio reversal in Poland. *Arch Sex Behav*. 1988 Dec;17(6):547-8. PMID: 3265612.

Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. *Br Med J*. 1970 May 23;1(5707):439-43. PMID: 5420206.

Goldman M. Spring 2008 - Stat C141/ Bioeng C141 - Statistics for Bioinformatics. Course Website:
<http://www.stat.berkeley.edu/users/hhuang/141C-2008.html>. Section Website:
<http://www.stat.berkeley.edu/users/mgoldman>.

Gómez-Gil E, Trilla García A, Godás Sieso T, Halperin Rabinovich I, Puig Domingo M, Vidal Hagemeijer A, Peri Nogués JM. Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand. *Actas Esp Psiquiatr*. 2006 Sep-Oct;34(5):295-302. Spanish. PMID: 17117339.

Gómez-Gil E, Trilla A, Salamero M, Godás T, Valdés M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Arch Sex Behav*. 2009 Jun;38(3):378-92. Epub 2008 Feb 21. PMID: 18288600.

Gómez-Gil E, Esteva I, Almaraz M, Pasaro E, Segovia S, Guillamon A. Familiality of gender identity disorder in non-twin siblings. *Arch Sex Behav*. 2010 Apr;39(2):546-52. Epub 2009 Jul 29. PMID: 19639402.

Gómez-Gil E, Esteva I, Carrasco R, Almaraz MC, Pasaro E, Salamero M, Guillamon A. Birth order and ratio of brothers to sisters in Spanish transsexuals. *Arch Sex Behav*. 2011 Jun;40(3):505-10. Epub 2010 Mar 16. PMID: 20232130.

A-Gómez-Gil E, Gómez A, Cañizares S, Guillamón A, Rametti G, Esteva I, Vázquez A, Salamero-Baró M. Clinical utility of the Bem Sex Role Inventory (BSRI) in the Spanish transsexual and nontranssexual population. *J Pers Assess*. 2012;94(3):304-9. Epub 2012 Jan 13. PMID: 22242861.

B-Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*. 2012 May;37(5):662-70. Epub 2011 Sep 19. PMID: 21937168.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Qual Life Res*. 2014 Mar;23(2):669-76. Epub 2013 Aug 13. PMID: 23943260.

Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res*. 2005;64 Suppl 2:31-6. PMID: 16286768.

A-Gooren L, Giltay E. Men and women, so different, so similar: observations from cross-sex hormone treatment of transsexual subjects. *Andrologia*. 2014 Jun;46(5):570-5. Epub 2013 May 19. PMID: 23682909.

B-Gooren L. Management of female-to-male transgender persons: medical and surgical management, life expectancy. *Curr Opin Endocrinol Diabetes Obes*. 2014 Jun;21(3):233-8. PMID: 24755998.

C-Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross-sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. *Eur J Endocrinol*. 2014 Jun;170(6):809-19. Epub 2014 Mar 10. PMID: 24616414.

D-Gooren L, Lips P. Conjectures concerning cross-sex hormone treatment of aging transsexual persons. *J Sex Med*. 2014 Aug;11(8):2012-9. Epub 2014 Apr 29. PMID: 24775178.

E-Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia*. 2014 Dec;46(10):1156-60. Epub 2013 Dec 12. PMID: 24329588.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebleux S, Penochet J, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lançon C, Bonierbale M. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med*. 2012 Feb;9(2):531-41. Epub 2011 Dec 6. PMID: 22145968.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet J, Pringuey D, Albarel F, Morange I, Bonierbale M, Lançon C, Auquier P. Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis*. 2013 Nov;201(11):996-1000. PMID: 24177489.

Grant JE, Flynn M, Odlaug BL, Schreiber LR. Personality disorders in gay, lesbian, bisexual, and transgender chemically dependent patients. *Am J Addict*. 2011 Sep-Oct;20(5):05-11. Epub 2011 Jul 18. PMID: 21838838.

Green R. Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res*. 1998 May;10 Suppl 1:S22-4. PMID: 9669217.

Greenberg G, Frank G. Response set in the Tennessee Department of Mental Health Self Concept Scale. *J Clin Psychol*. 1965 Jul;21:287-8. PMID: 14332192.

Greenberg RP, Laurence L. A comparison of the MMPI results for psychiatric patients and male applicants for transsexual surgery. *J Nerv Ment Dis*. 1981 May;169(5):320-3. PMID: 7217944.

Gurtman MB. Interpersonal Problems and the Psychotherapy Context: The Construct Validity of the Inventory of Interpersonal Problems. *Psychological Assessment*. 1996; 8 (3):241-55. (Not in PubMed)

Guadamuz TE, Wimonasate W, Varangrat A, Phanuphak P, Jommaroeng R, McNicholl JM, Mock PA, Tappero JW, van Griensven F. HIV prevalence, risk behavior, hormone use and surgical history among transgender persons in Thailand. *AIDS Behav*. 2011 Apr;15(3):650-8. PMID: 21104008.

A-Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008 Apr 26;336(7650):924-6. PMID: 18436948.

B-Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008 May 10;336(7651):995-8. PMID: 18456631.

C-Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. *BMJ*. 2008 May 10;336(7652): 1049-51. Erratum in: *BMJ*. 2008 Jun 21;336(7658). PMID: 18467413.

A-Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64(4):407-14. PMID: 21634461.

B-Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence study limitations (risk of bias). *J Clin Epidemiol*. 2011 Apr;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017. Epub 2011 Jan 19. PMID: 21247734.

C-Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence publication bias. *J Clin Epidemiol*. 2011 Dec;64(12):1277-82. Epub 2011 Jul 30. PMID: 21802904.

D-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence inconsistency. *J Clin Epidemiol*. 2011 Dec;64(12):1294-302. Epub 2011 Jul 31. PMID: 21803546.

E-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence indirectness. *J Clin Epidemiol*. 2011 Dec;64(12):1303-10. Epub 2011 Jul 30. PMID: 21802903.

Haas AP, Eliason M, Mays VM, Mathy RM, Cochran SD, D'Augelli AR, Silverman MM, Fisher PW, Hughes T, Rosario M, Russell ST, Malley E, Reed J, Litts DA, Haller E, Sell RL, Remafedi G, Bradford J, Beautrais AL, Brown GK, Diamond GM, Friedman MS, Garofalo R, Turner MS, Hollibaugh A, Clayton PJ. Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: review and recommendations. *J Homosex*. 2011;58(1):10-51. PMID: 21213174.

Hage JJ, De Graaf FH. Addressing the ideal requirements by free flap phalloplasty: some reflections on refinements of technique. *Microsurgery*. 1993;14(9):592-8. PMID: 8289643.

Hage JJ, Karim RB. Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plast Reconstr Surg*. 2000 Mar;105(3):1222-7. PMID: 10724285.

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatr Scand*. 2000 Oct;102(4):276-81. PMID: 11089727.

Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry*. 2009 Jan 1;65(1):93-6. Epub 2008 Oct 28. PMID: 18962445.

Hathaway S, Briggs P. Some normative data on new MMPI scales. *J Clin Psychol*. 1957 Oct;13(4):364-8. PMID: 13463138.

Hathaway SR, Reynolds PC, Monachesi ED. Follow-up of the later careers and lives of 1,000 boys who dropped out of high school. *J Consult Clin Psychol*. 1969 Jun;33(3):370-80. PMID: 4389336.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94:3132-54. PMID: 19509099.

Hembree WC. Guidelines for pubertal suspension and gender reassignment for transgender adolescents. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):725-32. PMID: 22051008.

Hepp U, Klaghofer R, Burkhard-Kübler R, Buddeberg C. [Treatment follow-up of transsexual patients. A catamnestic study]. *Nervenarzt*. 2002 Mar;73(3):283-8. German. PMID: 11963265.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. *J Psychosom Res*. 2005 Mar;58(3):259-61. PMID: 15865950.

Case 7:16-cv-00108-D Document 26 Filed 10/21/16 Page 709 of 919 PageID 1166
Herbst J, Jacobs E, Finlayson T, McKleroy W, Neumann H, Crepaz N. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. *AIDS Behav.* 2008 Jan;12(1):1-17. Epub 2007 Aug 13. PMID: 17694429.

Heresová J, Pobisová Z, Hampl R, Stárka L. Androgen administration to transsexual women. II. Hormonal changes. *Exp Clin Endocrinol.* 1986 Dec;88(2):219-23. PMID: 3556412.

Hormonal changes. *Exp Clin Endocrinol.* 1986 Dec;88(2):219-23. PMID: 3556412.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int.* 2014 Nov 21;111(47):795-801. PMID: 25487762.

A-Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med.* 2014 Jan;11(1):119-26. Epub 2013 Oct 28. PMID: 24344788.

B-Heylens G, Elaut E, Kreukels BP, Paap MC, Cerwenka S, Richter-Appelt H, Cohen-Kettenis PT, Haraldsen I, De Cuypere G. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. *Br J Psychiatry.* 2014 Feb;204(2):151-6. Epub 2013 May 9. PMID: 23869030.

HHS-HP: US Department of Health and Human Services. Lesbian, gay, bisexual and transgender health: objectives. Healthy People 2020. www.healthypeople.gov/2020/topics/objectives2020/overview.aspx?topicid=25.

HHS-2011: US Department of Health and Human Services. Affordable Care Act to improve data collection, reduce health disparities. www.hhs.gov/news/press/2011pres/06/20110629a.html.

Hines M, Ahmed SF, Hughes IA. Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. *Arch Sex Behav.* 2003 Apr;32(2):93-101. PMID: 12710824.

Hoekzema E, Schagen SE, Kreukels BP, Veltman DJ, Cohen-Kettenis PT, Delemarre-van de Waal H, Bakker J. Regional volumes and spatial volumetric distribution of gray matter in the gender dysphoric brain. *Psychoneuroendocrinology*. 2015 May;55:59-71. Epub 2015 Jan 30. PMID: 25720349.

Hoenig J, Kenna J, Youd A. A follow-up study of transsexualists: social and economic aspects. *Psychiatr Clin (Basel)*. 1970;3(2):85-100. PMID: 5424767.

Hoenig J, Kenna JC, Youd A. Surgical treatment for transsexualism. *Acta Psychiatr Scand*. 1971;47(1):106-33 or 36. PMID: 5096332 or 5148350.

Hoenig J, Kenna J. Epidemiological aspects of transsexualism. *Psychiatr Clin (Basel)*. 1973;6(2):65-80. PMID: 4705331.

Hoffman B. An Overview of Depression among Transgender Women. *Depress Res Treat*. 2014;2014:394283. Epub 2014 Mar 13. PMID: 24744918.

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009 Jan 21;(1):MR000006. PMID: 19160345.

Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ*. 2010 Mar 23;340:c723. PMID: 20332510.

Hopewell S, Hirst A, Collins GS, Mallett S, Yu LM, Altman DG. Reporting of participant flow diagrams in published reports of randomized trials. *Trials*. 2011 Dec 5;12:253. PMID: 22141446.

Horbach S, Bouman M, Smit J, Özer M, Buncamper M, Mullender M. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med*. 2015 Jun;12(6):1499-512. Epub 2015 Mar 26. PMID: 25817066.

Horowitz LM, Rosenberg SE, Baer BA, Ureño G, Villaseñor VS. Inventory of interpersonal problems: psychometric properties and clinical applications. *J Consult Clin Psychol*. 1988 Dec;56(6):885-92. PMID: 3204198.

Hoshiai M, Matsumoto Y, Sato T, Ohnishi M, Okabe N, Kishimoto Y, Terada S, Kuroda S. Psychiatric comorbidity among patients with gender identity disorder. *Psychiatry Clin Neurosci*. 2010 Oct;64(5):514-9. Epub 2010 Aug 19. PMID: 20727112.

A-Hunt DD, Hampson JL. Follow-up of 17 biologic male transsexuals after sex-reassignment surgery. *Am J Psychiatry*. 1980 Apr;137(4):432-8. PMID: 7361928.

B-Hunt DD, Hampson JL. Transsexualism: a standardized psychosocial rating format for the evaluation of results of sex reassignment surgery. *Arch Sex Behav*. 1980 Jun;9(3):255-63. PMID: 7396697.

Hunt DD, Carr JE, Hampson JL. Cognitive correlates of biologic sex and gender identity in transsexualism. *Arch Sex Behav*. 1981 Feb;10(1):65-77. PMID: 7011255.

Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, T'Sjoen G. Karyotyping, is it worthwhile intranssexualism? *J Sex Med*. 2011 Feb;8(2):475-8. Epub 2010 Nov 29. PMID: 21114769.

A-Imperato-McGinley J. 5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature. *Adv Exp Med Biol*. 2002;511:121-31; discussion 131-4. PMID: 12575759.

B-Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5 alpha-reductase-2 deficiency. *Mol Cell Endocrinol*. 2002 Dec 30;198(1-2):51-9. PMID: 12573814.

Insel T. Director's Blog: Transforming Diagnosis. April 29, 2013.
<http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml>.

Insel T. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry*. 2014 Apr;171(4):395-7. PMID: 24687194.

IOM 2011 Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. Institute of Medicine (IOM). (Study Sponsor: The National Institutes of Health). The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Issued March 31, 2011. <http://thefenwayinstitute.org/documents/lgbthealthreportbriefembargoed.pdf>.

Jackson PA. Thai research on male homosexuality and transgenderism and the cultural limits of Foucaultian analysis. *J Hist Sex*. 1997 Jul;8(1):52-85. PMID: 11619530.

Jackson, Peter A.. An explosion of Thai identities: peripheral genders and the limits of queer theory. *Culture, Health, & Sexuality*, 2000;2(4):405-24. Taylor & Francis. (Not in PubMed)

Jackson PA. Pre-gay, post-queer: Thai perspectives on proliferating gender/sex diversity in Asia. *J Homosex*. 2001;40(3-4):1-25. PMID: 11386329.

Jacobeit J, Gooren L, Schulte H. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. *Eur J Endocrinol*. 2009 Nov;161(5):795-8. Epub 2009 Sep 11. PMID: 19749027.

Jacobs, S-E, Thomas W, and Lang S (Eds.). (1997). *Two-spirit people: Native American gender identity, sexuality, and spirituality*. Urbana: University of Illinois Press.

Jain A, Bradbeer C. Gender identity disorder: treatment and post-transition care in transsexual adults. *Int J STD AIDS*. 2007 Mar;18(3):147-50. PMID: 17362542.

Case 7:16-cv-00108-0 Document 26 Filed 10/21/16 Page 704 of 919 PageID 1170

Jarolím L, Sedý J, Schmidt M, Nanka O, Foltán R, Kawaciuk I. Gender reassignment surgery in male-to-female transsexuals: A retrospective 5-mo follow-up study with clinical markers. *J Sex Med*. 2009 Jun;6(6):1635-44. Epub 2009 Mar 30. PMID: 19473463.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. *Arch Sex Behav*. 2010 Dec;39(6):1429-37. Epub 2009 Oct 9. PMID: 19816764.

Jokić-Begić N, Lauri Korajlija A, Jurin T. Psychosocial adjustment to sex reassignment surgery: a qualitative examination and personal experiences of six transsexual persons in Croatia. *Scientific World Journal*. 2014;2014:960745. Epub 2014 Mar 25. PMID: 24790589.

Joseph A, Shabir I, Marumadi E, Dada R, Ammini A, Mehta M. Psychosexual outcomes in three siblings with partial androgen insensitivity syndrome: impact of nature versus nurture. *J Pediatr Endocrinol Metab*. 2013;26(9-10):915-20. PMID: 23729553.

Judge C, O'Donovan C, Callaghan G, Gaoatswe G, O'Shea D. Gender dysphoria - prevalence and co-morbidities in an Irish adult population. *Front Endocrinol (Lausanne)* 2014;5:87. Epub 2014 Jun 13. PMID: 24982651.

Jürgensen M, Hiort O, Holterhus PM, Thyen U. Gender role behavior in children with XY karyotype and disorders of sex development. *Horm Behav*. 2007 Mar;51(3):443-53. Epub 2007 Jan 12. PMID: 17306800.

Keenan JP, Wheeler MA, Gallup GG Jr, Pascual-Leone A. Self-recognition and the right prefrontal cortex. *Trends Cogn Sci*. 2000 Sep;4(9):338-344. PMID: 10962615.

Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol*. 1997 Dec;104(12):1374-9. PMID: 9422015.

Khan L. Transgender health at the crossroads: legal norms, insurance markets, and the threat of healthcare reform. *Yale J Health Policy Law Ethics*. 2011 Summer;11(2):375-418. PMID: 22136012.

Khandelwal A, Agarwal A, Jiloha RC. A 47,XXY female with gender identity disorder. *Arch Sex Behav*. 2010 Oct;39(5):1021-3. PMID: 20464469.

Knight R. Fragmentation, fluidity, and transformation: nonlinear development in middle childhood. *Psychoanal Study Child*. 2011;65:19-47. PMID: 26027138.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. *Arch Sex Behav*. 1987 Dec;16(6):511-22. PMID: 3426393.

Kockott G, Fahrner EM. Male-to-female and female-to-male transsexuals: a comparison. *Arch Sex Behav*. 1988 Dec;17(6):539-46. PMID: 3223814.

Kohlberg, L. "A Cognitive-Developmental Analysis of Children's Sex-Role Concepts and Attitudes." In E. E. Maccoby (ed.). *The Development of Sex Differences*. Stanford, Calif.: Stanford University Press, 1966.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. *Psychopathology*. 2008;41(2):96-100. Epub 2007 Nov 23. PMID: 18033979.

Krege S, Bex A, Lümnen G, Rübber H. Male-to-female transsexualism: a technique, results and long-term follow-up in 66 patients. *BJU Int*. 2001 Sep;88(4):396-402. PMID: 11564029.

Kreukels B, Haraldsen, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis P. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry*. 2012 Aug;27(6):445-50. Epub 2010 Jul 9. PMID: 20620022.

Kröhn W, Bertermann H, Wand H, Wille R. [Transsexualism: a long-term follow-up after sex reassignment surgery (author's transl)]. *Nervenarzt*. 1981 Jan;52(1):26-31. PMID: 7219610.

Kronawitter D, Gooren LJ, Zollver H, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. Effects of transdermal testosterone or oral dydrogesterone on hypoactive sexual desire disorder in transsexual women: results of a pilot study. *Eur J Endocrinol*. 2009 Aug;161(2): 363-8. Epub 2009 Jun 4. PMID: 19497984.

Kruijver FP, Fernández-Guasti A, Fodor M, Kraan EM, Swaab DF. Sex differences in androgen receptors of the human mamillary bodies are related to endocrine status rather than to sexual orientation or transsexuality. *J Clin Endocrinol Metab*. 2001 Feb;86(2):818-27. PMID: 11158052.

Kuiper B, Cohen-Kettenis P. Sex reassignment surgery: a study of 141 Dutch transsexuals. *Arch Sex Behav*. 1988 Oct;17(5):439-57. PMID: 3219066.

Kuhn A, Hildebrand R, Birkhäuser M. Do transsexuals have micturition disorders? *Eur J Obstet Gynecol Reprod Biol*. 2007 Apr;131(2):226-30. Epub 2006 May 5. PMID: 16678333.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril*. 2009 Nov;92(5):1685-1689.e3. Epub 2008 Nov 6. PMID: 18990387.

Kuhn A, Santi A, Birkhäuser M. Vaginal prolapse, pelvic floor function, and related symptoms 16 years after sex reassignment surgery in transsexuals. *Fertil Steril*. 2011 Jun;95(7):2379-82. Epub 2011 Apr 2. PMID: 21458798.

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ*. 1998 Oct 31;317(7167):1185-90. PMID: 9794851.

Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):MR000012. Update in: *Cochrane Database Syst Rev*. 2011; (4) MR000012. PMID: 17443633.

Kuper LE, Nussbaum R, Mustanski B. Exploring the diversity of gender and sexual orientation identities in an online sample of transgender individuals. *J Sex Res.* 2012;49(2-3):244-54. Epub 2011 Jul 28. PMID: 21797716.

Lader EW, Cannon CP, Ohman EM, Newby LK, Sulmasy DP, Barst RJ, Fair JM, Flather M, Freedman JE, Frye RL, Hand MM, Jesse RL, Van de Werf F, Costa F; American Heart Association. The clinician as investigator: participating in clinical trials in the practice setting: Appendix 2: statistical concepts in study design and analysis. *Circulation.* 2004 Jun 1;109(21):e305-7. PMID: 15173053.

Lament C. Transgender Children: Conundrums and Controversies A Introduction to the Section. *Psychoanal Study Child* 2014;68:13-27. PMID: 26173324.

Lancet Editorial-No Authors . Health of lesbian, gay, bisexual, and transgender populations. *Lancet.* 2011 April 9;377: 1211. PMID:2 1481690.

Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand.* 1998 Apr;97(4):284-9. PMID: 9570489.

Lang, S. (1998). *Men as Women, Women as Men: Changing Gender in Native American Cultures*. Austin, TX: University of Texas Press.

Lang RJ, Vernon PE. Dimensionality of the perceived self: the Tennessee Self Concept Scale. *Br J Soc Clin Psychol.* 1977 Nov;16(4):363-71. PMID: 588892.

Lawrence AA. Changes in sexual orientation in six male-to-female (MtF) transsexuals. *Arch Sex Behav.* 1999 Dec;28(6):581-3. PMID: 10650442.

Lawrence A. Sexuality before and after male-to-female sex reassignment surgery. *Arch Sex Behav.* 2005 Apr;34(2):147-66. PMID: 15803249.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Arch Sex Behav.* 2006 Dec;35(6):717-27. Epub 2006 Nov 16. PMID: 17109225.

A-Lawrence AA. Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. *Arch Sex Behav.* 2010 Apr;39(2):514-45. Epub 2010 Feb 6. PMID: 20140487.

B-Lawrence AA. Societal individualism predicts prevalence of nonhomosexual orientation in male-to-female transsexualism. *Arch Sex Behav.* 2010 Apr;39(2):573-83. Epub 2008 Dec 9. PMID: 19067152.

Leavitt F, Berger JC, Hoeppner JA, Northrop G. Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis.* 1980 Nov;168(11):693-7. PMID: 6255090.

A-Leclère F, Casoli V, Weigert R. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med.* 2015 Jul;12(7):1655-6. Epub 2015 Jun 11. PMID: 26096230.

B-Leclère FM, Casoli V, Weigert R. Vaginoplasty in Male-to-Female Transsexual Surgery: A Training Concept Incorporating Dissection Room Experience to Optimize Functional and Cosmetic Results. *J Sex Med.* 2015 Oct;12(10):2074-83. PMID: 26481600.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. *Endocr Pract.* 2013 Jul-Aug;19(4):644-50. PMID: 23512380.

Lindemalm G, Körlin D, Uddenberg N. Long-term follow-up of "sex change" in 13 male-to-female transsexuals. *Arch Sex Behav*. 1986 Jun;15(3):187-210. PMID: 3729700.

Lindemalm G, Körlin D, Uddenberg N. Prognostic factors vs. outcome in male-to-female transsexualism. A follow-up study of 13 cases. *Acta Psychiatr Scand*. 1987 Mar;75(3):268-74. PMID: 3591409.

Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav*. 1975 Nov;4(6):639-56. PMID: 1212093.

Lioudaki E, Ganotakis ES, Mikhailidis DP, Nair DR. The estrogenic burden on vascular risk in male-to-female transsexuals. *Curr Pharm Des*. 2010;16(34):3815-22. PMID: 21128891

Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, da Graça Borges Fortes M, Petry AR, Silveira E, Henriques AA. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. *Arch Sex Behav*. 2006 Dec;35(6):711-5. PMID: 17075731.

Lothstein LM. The aging gender dysphoria (transsexual) patient. *Arch Sex Behav*. 1979 Sep;8(5):431-44. PMID: 496624.

Lothstein LM, Roback H. Black female transsexuals and schizophrenia: a serendipitous finding? *Arch Sex Behav*. 1984 Aug;13(4):371-86. PMID: 6487080.

Lothstein LM. Psychological testing with transsexuals: a 30-year review. *J Pers Assess*. 1984 Oct;48(5):500-7. PMID: 6389823.

Maccoby EE. The role of gender identity and gender constancy in sex-differentiated development. *New Dir Child Dev*. 1990 Spring;(47):5-20. PMID: 2194142.

Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, Cartigny M, Pienkowski C, Polak M, Skordis N, Mazen I, Ocal G, Berberoglu M, Reynaud R, Baumann C, Cabrol S, Simon D, Kayemba-Kay's K, De Kerdanet M, Kurtz F, Leheup B, Heinrichs C, Tenoutasse S, Van Vliet G, Grütters A, Eunice M, Ammini AC, Hafez M, Hochberg Z, Einaudi S, Al Mawlawi H, Nuñez CJ, Servant N, Lumbroso S, Paris F, Sultan C. Phenotypical, biological, and molecular heterogeneity of 5 α -reductase deficiency: an extensive international experience of 55 patients. *J Clin Endocrinol Metab*. 2011 Feb;96(2):296-307. Epub 2010 Dec 8. PMID: 21147889.

Marks I, Green R, Mataix-Cols D. Adult gender identity disorder can remit. *Compr Psychiatry*. 2000 Jul-Aug;41(4):273-5. PMID: 10929795.

Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: A systematic review of the literature. *Int Rev Psychiatry*. 2015 Sep 2:1-12. [Epub ahead of print]. PMID: 26329283.

Matarazzo B, Barnes S, Pease J, Russell L, Hanson J, Soberay K, Gutierrez P. Suicide risk among lesbian, gay, bisexual, and transgender military personnel and veterans: what does the literature tell us? *Suicide Life Threat Behav*. 2014 Apr;44(2):200-17. Epub 2014 Feb 3. PMID: 24494604.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. *Br J Psychiatry*. 1988 Apr;152:550-3. PMID: 3167409.

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. *Br J Psychiatry*. 1990 Aug;157:261-4. PMID: 2224377.

McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993 Mar;31(3):247-63. PMID: 8450681.

McHugh PR, Slavney PR. Mental illness comprehensive evaluation or checklist? *N Engl J Med*. 2012 May 17;366(20):1853-5. PMID: 22591291.

Meads C, Pennant M, McManus J, Bayliss S. West Midlands Health Technology Assessment Collaboration. A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. *Health Technology Assessment Database*. 2009. No.3. www.birmingham.ac.uk/Documents/college-mds/haps/projects/WMHTAC/REPreports/2009/LGBThealth030409finalversion.pdf.

Medraś M, Józków P. Transsexualism diagnostic and therapeutic aspects. *Endokrynol Pol*. 2010 Jul-Aug;61(4):412-6. PMID: 20806188.

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. *Sexual and Relationship Therapy*. 2007 Feb; 22(1):77-81. (Not in PubMed)

Melendez RM, Exner TA, Ehrhardt AA, Dodge B, Remien RH, Rotheram-Borus MJ, Lightfoot M, Hong D. Health and health care among male-to-female transgender persons who are HIV positive. *Am J Public Health*. 2006 Jun;96(6):1034-7. Epub 2005 Aug 30. PMID: 16131645.

Mepham N, Bouman W, Arcelus J, Hayter M, Wylie K. People with gender dysphoria who self-prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. *J Sex Med*. 2014 Dec;11(12):2995-3001. Epub 2014 Sep 11. PMID: 25213018.

Meriggiola M, Jannini E, Lenzi A, Maggi M, Manieri C. Endocrine treatment of transsexual persons: an App. 707

Meriggiola M, Berra M. Long-term cross-sex hormone treatment is safe in transsexual subjects. *Asian J Androl*. 2012 Nov;14(6):813-4. Epub 2012 Aug 27. PMID: 22922319.

Meriggiola M, Berra M. Safety of hormonal treatment in transgenders. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):565-9. PMID: 24468759.

A-Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):597-606. Epub 2015 Mar 25. PMID: 25692791.

B-Meriggiola MC, Gava G. Endocrine care of transpeople part II. A review of cross-sex hormonal treatments, outcomes and adverse effects in transwomen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):607-15. Epub 2015 Mar 25. PMID: 25692882.

Meyer J, Knorr N, Blumer D. Characterization of a self-designated transsexual population. *Arch Sex Behav* 1971 Sep;1(3):219-30. PMID: 24179067.

A-Meyer JK. Sex assignment and reassignment: intersex and gender identity disorders. Foreword. *Clin Plast Surg*. 1974 Apr;1(2):199-200. PMID: 4426156.

B-Meyer JK. Psychiatric considerations in the sexual reassignment of non-intersex individuals. *Clin Plast Surg*. 1974 Apr;1(2):275-83. PMID: 4426161.

C-Meyer JK, Hoopes JE. The gender dysphoria syndromes. A position statement on so-called "transsexualism". *Plast Reconstr Surg*. 1974 Oct;54(4):444-51. PMID: 4416283.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. *Arch Gen Psychiatry*. 1979 Aug;36(9): 1010-5. PMID: 464739.

Meyer WJ, Finkelstein JW, Stuart CA, Webb A, Smith ER, Payer AF, Walker PA. Physical and hormonal evaluation of transsexual patients during hormonal therapy. *Arch Sex Behav*. 1981 Aug;10(4):347-56. PMID: 6794543.

Meyer WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav* 1986 Apr;15(2):121-38. PMID: 22051002.

Meyer-Bahlburg HF. Gender outcome in 46,XY complete androgen insensitivity syndrome: comment on T'Sjoen et al. (2010). *Arch Sex Behav*. 2010 Dec;39(6):1221-4. PMID: 20552263.

Meyer-Bahlburg HF. Gender monitoring and gender reassignment of children and adolescents with a somatic disorder of sex development. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):639-49. PMID: 22051002. Epub 2011 Sep 23.

Miach PP, Berah EF, Butcher JN, Rouse S. Utility of the MMPI-2 in assessing gender dysphoric patients. *J Pers Assess*. 2000 Oct;75(2):268-79. PMID: 11020144.

Michel A, Mormont C, Legros JJ. A psycho-endocrinological overview of transsexualism. *Eur J Endocrinol*. 2001 Oct;145(4):365-76. PMID: 11580991.

Michel A, Ansseau M, Legros J, Pitchot W, Cornet J, Mormont C. Comparisons of two groups of sex-change applicants based on the MMPI. *Psychol Rep* 2002 Aug;91(1):233-40. PMID: 12353786.

Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*. 2003; May-June. Report 33, No. 3: 19-28. PMID: 12854452.

Miller FG. Equipoise and the Ethics of Clinical Research Revisited. *The American Journal of Bioethics*. 2006; 6:4, 59-61. PMID: 16885110.

Miller PB, Weijer C. Trust based obligations of the state and physician-researchers to patient-subjects. *J Med Ethics*. 2006 Sep;32(9):542-7. PMID: 16943338.

A-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010 Mar 23;340:c869. PMID: 20332511.

B-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG; Consolidated Standards of Reporting Trials Group. CONSORT 2010 Explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010 Aug;63(8):e1-37. Epub 2010 Mar 25. Erratum in *J Clin Epidemiol*. 2012 Mar;65(3):351. PMID: 20346624.

Monstrey S, Hoebeke P, Selvaggi G, Ceulemans P, Van Landuyt K, Blondeel P, Hamdi M, Roche N, Weyers S, De Cuypere G. Penile reconstruction: is the radial forearm flap really the standard technique? *Plast Reconstr Surg*. 2009 Aug;124(2):510-8. PMID: 19644267.

Monstrey S, Ceulemans P, Hoebeke P. Sex Reassignment Surgery in the Female-to-Male Transsexual. *Semin Plast Surg*. 2011 Aug;25(3):229-44. PMID: 22851915.

Moreno-Pérez O, Esteva De Antonio I; Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). [Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN)]. *Endocrinol Nutr*. 2012 Jun-Jul;59(6):367-82. Epub 2012 Apr 26. *Appis* 710

Moser C. Blanchard's Autogynephilia Theory: a critique. *J Homosex*. 2010;57(6):790-809. PMID: 20582803.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. *J Sex Med*. 2012 Mar;9(3):743-50. Epub 2011 Dec 21. PMID: 22188877.

Motmans J, Ponnet K, De Cuypere G. Sociodemographic characteristics of trans persons in Belgium: A secondary data analysis of medical, state, and social data. *Arch Sex Behav*. 2015 Jul;44(5):1289-99. Epub 2014 Oct 10. PMID: 25300904.

Mueller A, Haeberle L, Zollner H, Claassen T, Kronawitter D, Oppelt P, Cupisti S, Beckmann M, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med*. 2010 Sep;7(9):3190-8. PMID: 20584125.

Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010 Feb;72(2):214-31. Epub 2009 May 16. PMID: 19473181.

Nanda S. The hijras of India: cultural and individual dimensions of an institutionalized third gender role. *J Homosex*. 1985 Summer;11(3-4):35-54. PMID: 4093603.

Nanda, S. (1999). *Neither man nor woman: The hijras of India*. Belmont, CA: Wadsworth Publishing.

Nanda S. (2014, 2nd edition) *Gender Diversity: Cross cultural variations*. Long Grove, IL: Waveland Press.

NIH-LGBT 2013: National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consolidation of the Institute of Medicine (IOM) report on the health of Lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf.

Nemoto T, Iwamoto M, Perngparn U, Areesantichai C, Kamitani E, Sakata M. HIV-related risk behaviors among kathoey (male-to-female transgender) sex workers in Bangkok, Thailand. *AIDS Care*. 2012;24(2):210-9. Epub 2011 Jul 25. PMID: 21780964.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. *Qual Life Res*. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. PMID: 16758113.

Newsom J. Latent variable. *USP 655 SEM. Winter 2015*. (Portland State quantitative methods) www.upa.pdx.edu/IOA/newsom/semclass/ho_latent.pdf.

Nieder T, Herff M, Cerwenka S, Preuss W, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Richter-Appelt H. Age of onset and sexual orientation in transsexual males and females. *J Sex Med*. 2011 Mar;8(3):783-91. Epub 2010 Dec 8. PMID: 21143416.

Nuttbrock L, Hwahng S, Bockting W, Rosenblum A, Mason M, Macri M, Becker J. Lifetime risk factors for HIV/sexually transmitted infections among male-to-female transgender persons. *J Acquir Immune Defic Syndr*. 2009 Nov 1;52(3):417-21. PMID: 19550351.

Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. Gender abuse, depressive symptoms, and HIV and other sexually transmitted infections among male-to-female transgender persons: a three-year prospective study. *Am J Public Health*. 2013 Feb;103(2):300-7. Epub 2012 Jun 14. Erratum in: *Am J Public Health*. 2015 Feb;105(2):e5. PMID: 22698023.

NZHTA 2002: Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

O’Gorman EC. A preliminary report on transsexualism in Northern Ireland. *Ulster Med J*. 1981;50(1):46–9. PMID: 7233635.

Okabe N, Sato T, Matsumoto Y, Ido Y, Terada S, Kuroda S. Clinical characteristics of patients with gender identity disorder at a Japanese gender identity disorder clinic. *Psychiatry Res*. 2008 Jan 15;157(1-3):315-8. Epub 2007 Oct 23. PMID: 17959255.

Olson J, Forbes C, Belzer M. Management of the transgender adolescent. *Arch Pediatr Adolesc Med*. 2011 Feb;165(2):171-6. PMID: 21300658.

Olsson SE, Jansson I, Moller A. Men as women. Experiences from five case after administrative, hormonal, and surgical treatment. *Nord J Psychiatry*. 1996;50(5):395-9. (Not in PubMed)

Olsson S, Möller A. On the incidence and sex ratio of transsexualism in Sweden, 1972-2002. *Arch Sex Behav*. 2003 Aug;32(4):381-6. PMID: 12856899.

Olsson S, Möller A. Regret after sex reassignment surgery in a male-to-female transsexual: a long-term follow-up. *Arch Sex Behav*. 2006 Aug;35(4):501-6. Epub 2006 Aug 11. PMID: 16900416.

Operario D, Nemoto T. HIV in transgender communities: syndemic dynamics and a need for multicomponent interventions. *J Acquir Immune Defic Syndr*. 2010 Dec;55 Suppl 2:S91-3. PMID: 21406995.

Operario D, Nemoto T, Iwamoto M, Moore T. Unprotected sexual behavior and HIV risk in the context of primary partnerships for transgender women. *AIDS Behav*. 2011 Apr;15(3):674-82. PMID: 21604064.

Oster JM, Shastri P, Geyer C. Cerebral venous sinus thrombosis after gender reassignment surgery. *Gend Med*. 2010 Jun;7(3):270-5. PMID: 20638632.

Ott J, van Trotsenburg M, Kaufmann U, Schrögenderfer K, Haslik W, Huber JC, Wenzl R. Combined hysterectomy/salpingo-oophorectomy and mastectomy is a safe and valuable procedure for female-to-male transsexuals. *J Sex Med*. 2010 Jun;7(6):2130-8. Epub 2010 Mar 3. PMID: 20233279.

Paap MC, Meijer RR, Cohen-Kettenis PT, Richter-Appelt H, de Cuypere G, Kreukels BP, Pedersen G, Karterud S, Malt UF, Haraldsen IR. Why the factorial structure of the SCL-90-R is unstable: comparing patient groups with different levels of psychological distress using Mokken Scale Analysis. *Psychiatry Res*. 2012 Dec 30;200(2-3):819-26. Epub 2012 Apr 9. PMID: 22494703.

Palmer D, Dietsch A, Searl J. Endoscopic and stroboscopic presentation of the larynx in male-to-female transsexual persons. *J Voice*. 2012 Jan;26(1):117-26. Epub 2011 Apr 7. PMID: 21477987.

Palmer JR, Wise LA, Robboy SJ, Titus-Ernstoff L, Noller KL, Herbst AL, Troisi R, Hoover RN. Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology*. 2005 Jul;16(4):583-6. PMID: 15951681.

Palmer JR, Herbst AL, Noller KL, Boggs DA, Troisi R, Titus-Ernstoff L, Hatch EE, Wise LA, Strohsnitter WC, Hoover RN. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environ Health*. 2009 Aug 18;8:37. PMID: 19689815.

Pauly IB. The current status of the change of sex operation. *J Nerv Ment Dis*. 1968 Nov;147(5):460-71. PMID: 5726920.

Pauly IB. Outcome of sex reassignment surgery for transsexuals. *Aust N Z J Psychiatry* 1981 Mar;15(1):45-51. PMID: 6942832.

Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola M. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med.* 2014 Dec;11(12):3002-11. Epub 2014 Sep 24. PMID: 25250780.

Perez KM, Titus-Ernstoff L, Hatch EE, Troisi R, Wactawski-Wende J, Palmer JR, Noller K, Hoover RN; National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril.* 2005 Dec;84(6):1649-56. PMID: 16359959.

Perrone A, Cerpolini S, Maria Salfi N, Ceccarelli C, De Giorgi L, Formelli G, Casadio P, Ghi T, Pelusi G, Pelusi C, Meriggiola M. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. *J Sex Med.* 2009 Nov;6(11):3193-200. Epub 2009 Jun 29. PMID: 19570144.

Persson D. Unique challenges of transgender aging: implications from the literature. *J Gerontol Soc Work.* 2009 Aug-Sep;52(6):633-46. PMID: 19598043.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 1: conceptual and definitional issues in psychiatric diagnosis. *Philos Ethics Humanit Med.* 2012 Jan 13;7:3. PMID: 22243994.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 2: Issues of conservatism and pragmatism in psychiatric diagnosis. *Philos Ethics Humanit Med.* 2012 Jul 5;7:8. PMID: 22512887.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 3: issues of utility and alternative approaches in psychiatric diagnosis. *Philos Ethics Humanit Med.* 2012 May 23;7:9. PMID: 22621419.

Case 7:16-cv-01108-EB Document 26 Filed 10/21/16 Page 720 of 919 PageID 1186
Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn W, Le Bell SE, Mauch B, O'Donnell L, Parisi D, Pines A, Pines E, Pines J, Pines M, Pines N, Pines O, Pines P, Pines Q, Pines R, Pines S, Pines T, Pines U, Pines V, Pines W, Pines X, Pines Y, Pines Z, Pines AA, Pines AB, Pines AC, Pines AD, Pines AE, Pines AF, Pines AG, Pines AH, Pines AI, Pines AJ, Pines AK, Pines AL, Pines AM, Pines AN, Pines AO, Pines AP, Pines AQ, Pines AR, Pines AS, Pines AT, Pines AU, Pines AV, Pines AW, Pines AX, Pines AY, Pines AZ, Pines BA, Pines BB, Pines BC, Pines BD, Pines BE, Pines BF, Pines BG, Pines BH, Pines BI, Pines BJ, Pines BK, Pines BL, Pines BM, Pines BN, Pines BO, Pines BP, Pines BQ, Pines BR, Pines BS, Pines BT, Pines BU, Pines BV, Pines BW, Pines BX, Pines BY, Pines BZ, Pines CA, Pines CB, Pines CC, Pines CD, Pines CE, Pines CF, Pines CG, Pines CH, Pines CI, Pines CJ, Pines CK, Pines CL, Pines CM, Pines CN, Pines CO, Pines CP, Pines CQ, Pines CR, Pines CS, Pines CT, Pines CU, Pines CV, Pines CW, Pines CX, Pines CY, Pines CZ, Pines DA, Pines DB, Pines DC, Pines DD, Pines DE, Pines DF, Pines DG, Pines DH, Pines DI, Pines DJ, Pines DK, Pines DL, Pines DM, Pines DN, Pines DO, Pines DP, Pines DQ, Pines DR, Pines DS, Pines DT, Pines DU, Pines DV, Pines DW, Pines DX, Pines DY, Pines DZ, Pines EA, Pines EB, Pines EC, Pines ED, Pines EE, Pines EF, Pines EG, Pines EH, Pines EI, Pines EJ, Pines EK, Pines EL, Pines EM, Pines EN, Pines EO, Pines EP, Pines EQ, Pines ER, Pines ES, Pines ET, Pines EU, Pines EV, Pines EW, Pines EX, Pines EY, Pines EZ, Pines FA, Pines FB, Pines FC, Pines FD, Pines FE, Pines FF, Pines FG, Pines FH, Pines FI, Pines FJ, Pines FK, Pines FL, Pines FM, Pines FN, Pines FO, Pines FP, Pines FQ, Pines FR, Pines FS, Pines FT, Pines FU, Pines FV, Pines FW, Pines FX, Pines FY, Pines FZ, Pines GA, Pines GB, Pines GC, Pines GD, Pines GE, Pines GF, Pines GG, Pines GH, Pines GI, Pines GJ, Pines GK, Pines GL, Pines GM, Pines GN, Pines GO, Pines GP, Pines GQ, Pines GR, Pines GS, Pines GT, Pines GU, Pines GV, Pines GW, Pines GX, Pines GY, Pines GZ, Pines HA, Pines HB, Pines HC, Pines HD, Pines HE, Pines HF, Pines HG, Pines HH, Pines HI, Pines HJ, Pines HK, Pines HL, Pines HM, Pines HN, Pines HO, Pines HP, Pines HQ, Pines HR, Pines HS, Pines HT, Pines HU, Pines HV, Pines HW, Pines HX, Pines HY, Pines HZ, Pines IA, Pines IB, Pines IC, Pines ID, Pines IE, Pines IF, Pines IG, Pines IH, Pines II, Pines IJ, Pines IK, Pines IL, Pines IM, Pines IN, Pines IO, Pines IP, Pines IQ, Pines IR, Pines IS, Pines IT, Pines IU, Pines IV, Pines IW, Pines IX, Pines IY, Pines IZ, Pines JA, Pines JB, Pines JC, Pines JD, Pines JE, Pines JF, Pines JG, Pines JH, Pines JI, Pines JJ, Pines JK, Pines JL, Pines JM, Pines JN, Pines JO, Pines JP, Pines JQ, Pines JR, Pines JS, Pines JT, Pines JU, Pines JV, Pines JW, Pines JX, Pines JY, Pines JZ, Pines KA, Pines KB, Pines KC, Pines KD, Pines KE, Pines KF, Pines KG, Pines KH, Pines KI, Pines KJ, Pines KK, Pines KL, Pines KM, Pines KN, Pines KO, Pines KP, Pines KQ, Pines KR, Pines KS, Pines KT, Pines KU, Pines KV, Pines KW, Pines KX, Pines KY, Pines KZ, Pines LA, Pines LB, Pines LC, Pines LD, Pines LE, Pines LF, Pines LG, Pines LH, Pines LI, Pines LJ, Pines LK, Pines LL, Pines LM, Pines LN, Pines LO, Pines LP, Pines LQ, Pines LR, Pines LS, Pines LT, Pines LU, Pines LV, Pines LW, Pines LX, Pines LY, Pines LZ, Pines MA, Pines MB, Pines MC, Pines MD, Pines ME, Pines MF, Pines MG, Pines MH, Pines MI, Pines MJ, Pines MK, Pines ML, Pines MM, Pines MN, Pines MO, Pines MP, Pines MQ, Pines MR, Pines MS, Pines MT, Pines MU, Pines MV, Pines MW, Pines MX, Pines MY, Pines MZ, Pines NA, Pines NB, Pines NC, Pines ND, Pines NE, Pines NF, Pines NG, Pines NH, Pines NI, Pines NJ, Pines NK, Pines NL, Pines NM, Pines NN, Pines NO, Pines NP, Pines NQ, Pines NR, Pines NS, Pines NT, Pines NU, Pines NV, Pines NW, Pines NX, Pines NY, Pines NZ, Pines OA, Pines OB, Pines OC, Pines OD, Pines OE, Pines OF, Pines OG, Pines OH, Pines OI, Pines OJ, Pines OK, Pines OL, Pines OM, Pines ON, Pines OO, Pines OP, Pines OQ, Pines OR, Pines OS, Pines OT, Pines OU, Pines OV, Pines OW, Pines OX, Pines OY, Pines OZ, Pines PA, Pines PB, Pines PC, Pines PD, Pines PE, Pines PF, Pines PG, Pines PH, Pines PI, Pines PJ, Pines PK, Pines PL, Pines PM, Pines PN, Pines PO, Pines PP, Pines PQ, Pines PR, Pines PS, Pines PT, Pines PU, Pines PV, Pines PW, Pines PX, Pines PY, Pines PZ, Pines QA, Pines QB, Pines QC, Pines QD, Pines QE, Pines QF, Pines QG, Pines QH, Pines QI, Pines QJ, Pines QK, Pines QL, Pines QM, Pines QN, Pines QO, Pines QP, Pines QQ, Pines QR, Pines QS, Pines QT, Pines QU, Pines QV, Pines QW, Pines QX, Pines QY, Pines QZ, Pines RA, Pines RB, Pines RC, Pines RD, Pines RE, Pines RF, Pines RG, Pines RH, Pines RI, Pines RJ, Pines RK, Pines RL, Pines RM, Pines RN, Pines RO, Pines RP, Pines RQ, Pines RR, Pines RS, Pines RT, Pines RU, Pines RV, Pines RW, Pines RX, Pines RY, Pines RZ, Pines SA, Pines SB, Pines SC, Pines SD, Pines SE, Pines SF, Pines SG, Pines SH, Pines SI, Pines SJ, Pines SK, Pines SL, Pines SM, Pines SN, Pines SO, Pines SP, Pines SQ, Pines SR, Pines SS, Pines ST, Pines SU, Pines SV, Pines SW, Pines SX, Pines SY, Pines SZ, Pines TA, Pines TB, Pines TC, Pines TD, Pines TE, Pines TF, Pines TG, Pines TH, Pines TI, Pines TJ, Pines TK, Pines TL, Pines TM, Pines TN, Pines TO, Pines TP, Pines TQ, Pines TR, Pines TS, Pines TT, Pines TU, Pines TV, Pines TW, Pines TX, Pines TY, Pines TZ, Pines UA, Pines UB, Pines UC, Pines UD, Pines UE, Pines UF, Pines UG, Pines UH, Pines UI, Pines UJ, Pines UK, Pines UL, Pines UM, Pines UN, Pines UO, Pines UP, Pines UQ, Pines UR, Pines US, Pines UT, Pines UU, Pines UV, Pines UW, Pines UX, Pines UY, Pines UZ, Pines VA, Pines VB, Pines VC, Pines VD, Pines VE, Pines VF, Pines VG, Pines VH, Pines VI, Pines VJ, Pines VK, Pines VL, Pines VM, Pines VN, Pines VO, Pines VP, Pines VQ, Pines VR, Pines VS, Pines VT, Pines VU, Pines VV, Pines VW, Pines VX, Pines VY, Pines VZ, Pines WA, Pines WB, Pines WC, Pines WD, Pines WE, Pines WF, Pines WG, Pines WH, Pines WI, Pines WJ, Pines WK, Pines WL, Pines WM, Pines WN, Pines WO, Pines WP, Pines WQ, Pines WR, Pines WS, Pines WT, Pines WU, Pines WV, Pines WW, Pines WX, Pines WY, Pines WZ, Pines XA, Pines XB, Pines XC, Pines XD, Pines XE, Pines XF, Pines XG, Pines XH, Pines XI, Pines XJ, Pines XK, Pines XL, Pines XM, Pines XN, Pines XO, Pines XP, Pines XQ, Pines XR, Pines XS, Pines XT, Pines XU, Pines XV, Pines XW, Pines XX, Pines XY, Pines XZ, Pines YA, Pines YB, Pines YC, Pines YD, Pines YE, Pines YF, Pines YG, Pines YH, Pines YI, Pines YJ, Pines YK, Pines YL, Pines YM, Pines YN, Pines YO, Pines YP, Pines YQ, Pines YR, Pines YS, Pines YT, Pines YU, Pines YV, Pines YW, Pines YX, Pines YY, Pines YZ, Pines ZA, Pines ZB, Pines ZC, Pines ZD, Pines ZE, Pines ZF, Pines ZG, Pines ZH, Pines ZI, Pines ZJ, Pines ZK, Pines ZL, Pines ZM, Pines ZN, Pines ZO, Pines ZP, Pines ZQ, Pines ZR, Pines ZS, Pines ZT, Pines ZU, Pines ZV, Pines ZW, Pines ZX, Pines ZY, Pines ZZ.

PRO Guidance 2009: U.S. Department of Health and Human Services; Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). *Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labeling claims.* December 2009. <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf>.

Quirós C, Patrascioiu I, Mora M, Aranda GB, Hanzu FA, Gómez-Gil E, Godás T, Halperin I. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. *Endocrinol Nutr.* 2015 May;62(5):210-6. Epub 2015 Mar 16. PMID: 25790747.

Rachlin Katherine. Factors Which Influence Individual's Decisions When Considering Female-To-Male Genital Reconstructive Surgery. *IJT.* 1999 Jul-Sept;3(3). (Not in PubMed) <http://www.symposion.com/ijt/ijt990302.htm>
<http://www.iiav.nl/eazines/web/ijt/97-03/numbers/symposion/ijt990302.htm>

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. *Arch Sex Behav.* 1996 Oct;25(5):515-25. PMID: 8899143.

A-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Segovia S, Gomez Á, Guillamon A. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *J Psychiatr Res.* 2011 Feb;45(2):199-204. Epub 2010 Jun 8. PMID: 20562024.

B-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Zubiarre-Elorza L, Segovia S, Gomez Á, Guillamon A. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *J Psychiatr Res.* 2011 Jul;45(7):949-54. Epub 2010 Dec 30. PMID: 21195418.

Randell JB. Transvestitism and trans-sexualism. A study of 50 cases. *Br Med J.* 1959 Dec 26; 2(5164): 1448-52. PMID: 14436154.

Randell J. (1969). *Pre-operative and post-operative status of transsexuals* (Chapter 26) in Green R, Money J (eds):*Trans-sexualism and Sex reassignment*. Baltimore: Johns Hopkins Press.

Rappaport R. Intersex management: what is achieved and what is needed. Commentary to Thyen et al.: epidemiology and initial management of ambiguous genitalia at birth in Germany (*Horm Res*. 2006;66:195-203). *Horm Res*. 2006;66(4):204-5. Epub 2006 Jul 27. PMID: 16877871.

Reed HM. Aesthetic and functional male to female genital and perineal surgery: feminizing vaginoplasty. *Semin Plast Surg*. 2011 May;25(2):163-74. PMID: 22547974.

Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A. The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Arch Sex Behav*. 1999 Feb;28(1):71-89. PMID: 10097806.

Roback HB, Lothstein LM. The female mid-life sex change applicant: a comparison with younger female transsexuals and older male sex change applicants. *Arch Sex Behav*. 1986 Oct;15(5):401-15. PMID: 3789904.

Roscoe W. (1991). *The Zuni Man-Woman*. Albuquerque: University of New Mexico Press.

Roscoe, W. (1998). *Changing Ones: Third and Fourth Genders in Native North America*. New York: St. Martin's Press.

Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000 Apr-Jun;26(2):191-208. PMID: 10782451.

Ross MW, Wålinder J, Lundström B, Thuwe I. Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia. *Acta Psychiatr Scand*. 1981 Jan;63(1):75-82. PMID: 7234467.

Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Arch Sex Behav*. 1989 Apr;18(2):145-53. PMID: 2712690.

Rubin SO. Sex-reassignment surgery male-to-female. Review, own results and report of a new technique using the glans penis as a pseudoclitoris. *Scand J Urol Nephrol Suppl*. 1993;154:1-28. PMID: 8140401.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. *Arch Sex Behav*. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18. PMID: 25690443.

Russell ST, Ryan C, Toomey RB, Diaz RM, Sanchez J. Lesbian, gay, bisexual, and transgender adolescent school victimization: implications for young adult health and adjustment. *J Sch Health*. 2011 May;81(5):223-30. PMID: 21517860.

Safer J, Tangpricha V. Out of the shadows: it is time to mainstream treatment for transgender patients. *Endocr Pract*. 2008 Mar;14(2):248-50. PMID: 18308667.

Salkind MR. Beck depression inventory in general practice. *J R Coll Gen Pract*. 1969 Nov;18(88):267-71. PMID: 5350525.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun;66(4):371-2. PMID: 22624747.

Schaeffer CE. The Kutenai female berdache: Courier, guide, prophetess, and warrior. *Ethnohistory.* 1965;12 (3): 193–236. (Not in PubMed)

Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. *Arch Sex Behav.* 1998 Oct;27(5):475-92. PMID: 9795728.

Schroder M, Carroll RA. New women: Sexological outcomes of male-to-female gender reassignment surgery. *JSET.* 1999;24(3):137-46. (Not in PubMed)

Seal L, Franklin S, Richards C, Shishkareva A, Sinclair C, Barrett J. Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens. *J Clin Endocrinol Metab.* 2012 Dec;97(12):4422-8. Epub 2012 Oct 9. PMID: 23055547.

Selvaggi G, Monstrey S, Ceulemans P, T'Sjoen G, De Cuypere G, Hoebeke P. Genital sensitivity after sex reassignment surgery in transsexual patients. *Ann Plast Surg.* 2007 Apr;58(4):427-33. PMID: 17413887.

Selvaggi G, Bellringer J. Gender reassignment surgery: an overview. *Nat Rev Urol.* 2011 May;8(5):274-82. Epub 2011 Apr 12. PMID: 21487386.

Selvaggi G, Dhejne C, Landen M, Elander A. The 2011 WPATH Standards of Care and Penile Reconstruction in Female-to-Male Transsexual Individuals. *Adv Urol.* 2012;2012:581712. Epub 2012 May 14. PMID: 22654902.

Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. *Clin Breast Cancer.* 2011 Dec;11(6):417-9. Epub 2011 Aug 10. PMID: 21831723.

Shechner T. Gender identity disorder: a literature review from a developmental perspective. *Isr J Psychiatry Relat Sci*. 2010;47(2):132-8. PMID: 20733256.

Shields J, Cohen R, Glassman J, Whitaker K, Franks H, Bertolini I. Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *J Adolesc Health*. 2013 Feb;52(2):248-50. Epub 2012 Aug 15. PMID: 23332492.

Simopoulos E, Khin Khin E. Fundamental principles inherent in the comprehensive care of transgender inmates. *J Am Acad Psychiatry Law*. 2014;42(1):26-36. PMID: 24618516.

Slabbekoorn D, van Goozen SH, Sanders G, Gooren LJ, Cohen-Kettenis PT. The dermatoglyphic characteristics of transsexuals: is there evidence for an organizing effect of sex hormones. *Psychoneuroendocrinology*. 2000 May;25(4):365-75. PMID: 10725613.

Slabbekoorn D., Van Goozen S., Gooren L., Cohen-Kettenis P. Effects of Cross-Sex Hormone Treatment on Emotionality in Transsexuals. *IJT*. 2001 Jul-Sept; 5(3):20 pages.
http://www.symposion.com/ijt/ijtvo05no03_02.htm.

Slaby RG, Frey KS. Development of gender constancy and selective attention to same-sex models. *Child Dev*. 1975 Dec;46(4):849-56. PMID: 1201664.

Smilkstein G. The family APGAR: a proposal for a family function test and its use by physicians. *J Fam Pract*. 1978 Jun;6(6):1231-9. PMID: 660126.

Smilkstein G, Ashworth C, Montano D. Validity and reliability of the family APGAR as a test of family function. *J Fam Pract*. 1982 Aug;15(2):303-11. PMID:7097168.

Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2001

A-Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med*. 2005 Jan;35(1):89-99. PMID: 15842032.

B-Smith Y, van Goozen S, Kuiper A, Cohen-Kettenis P. Transsexual subtypes: clinical and theoretical significance. *Psychiatry Res*. 2005 Dec 15;137(3):151-60. Epub 2005 Nov 17. PMID: 16298429.

A-Sørensen T. A follow-up study of operated transsexual males. *Acta Psychiatr Scand*. 1981 May;63(5):486-503. PMID: 7315491.

B-Sørensen T. A follow-up study of operated transsexual females. *Acta Psychiatr Scand*. 1981 Jul;64(1):50-64. PMID: 7315494.

Sørensen T, Hertoft P. Male and female transsexualism: the Danish experience with 37 patients. *Arch Sex Behav*. 1982 Apr;11(2):133-55. PMID: 7125885.

Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

J Am Acad Child Adolesc Psychiatry. 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

Stieglitz KA. Development, risk, and resilience of transgender youth. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):192-206 Epub 2010 Mar 29. PMID: 20347346.

Stephens SC, Bernstein KT, Philip SS. Male to female and female to male transgender persons have different sexual risk behaviors yet similar rates of STDs and HIV. *AIDS Behav*. 2011 Apr;15(3):683-6. PMID: 20694509.

Stinson B. A study of twelve applicants for transsexual surgery. *Ohio State Med J*. 1972 Mar;68(3):245-9. PMID: 4401539.

Stojanovic B, Djordjevic ML. Anatomy of the clitoris and its impact on neophalloplasty (metoidioplasty) in female transgenders. *Clin Anat*. 2015 Apr;28(3):368-75. Epub 2015 Mar 4. PMID: 25740576.

Strauss B, Richter-Appelt H (1995) *Fragebogen zur Beurteilung des eigenen Körpers (FBek), Handanweisung*. Hogrefe, Göttingen Bern Toronto Seattle.

Stroumsa D. The state of transgender health care: policy, law, and medical frameworks. *Am J Public Health* . 2014 Mar;104(3):e31-8. Epub 2014 Jan 16. PMID: 24432926.

Sultan B. Transsexual prisoners: how much treatment is enough? *New Engl Law Rev*. 2003 Summer;37(4):1195-230. PMID: 15295855.

Sundbom E, Bodlund O. Prediction of outcome in transsexualism by means of the Defense Mechanism Test and multivariate modeling: a pilot study. *Percept Mot Skills*. 1999 Feb;88(1):3-20. PMID: 10214627.

Swaab DF. Sexual differentiation of the human brain: relevance for gender identity, transsexualism and sexual orientation. *Gynecol Endocrinol*. 2004 Dec;19(6):301-12. PMID: 15724806.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Suicidal ideation among patients with gender identity disorder. *Psychiatry Res*. 2011 Nov 30;190(1):159-62. Epub 2011 May 25. PMID: 21612827.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Factors predicting psychiatric co-morbidity in gender-dysphoric adults. *Psychiatry Res*. 2012 Dec 30;200(2-3):469-74. Epub 2012 Aug 9. PMID: 22884214.

Titus-Ernstoff L, Perez K, Hatch EE, Troisi R, Palmer JR, Hartge P, Hyer M, Kaufman R, Adam E, Strohsnitter W, Noller K, Pickett KE, Hoover R. Psychosexual characteristics of men and women exposed prenatally to diethylstilbestrol. *Epidemiology*. 2003 Mar;14(2):155-60. PMID: 12606880.

Torres A, Gómez-Gil E, Vidal A, Puig O, Boget T, Salamero M. Gender differences in cognitive functions and influence of sex hormones. *Actas Esp Psiquiatr*. 2006 Nov-Dec;34(6):408-15. Spanish. PMID: 17117339.

Tourbach SA, Hunter-Smith D, Morrison WA. Long anterior urethral reconstruction using a jejunal free flap. *J Plast Surg Hand Surg*. 2011 Feb;45(1):54-6. PMID: 21446801.

Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: lessons from female-to-male transsexuals (FMT) treated with pharmacological testosterone therapy. *J Sex Med*. 2010 Nov;7(11):3758-64. Epub 2010 Aug 16. PMID: 20722789.

Trentacosti AM. *Epoietin alpha: FDA overview of patient reported outcome (PRO) claims*. 2007. www.fda.gov/ohrms/dockets/ac/07/slides/2007-4315s1-09-FDA-Trentacosti.ppt.

Trum H, Hoebeke P, Gooren L. Sex reassignment of transsexual people from a gynecologist's and urologist's perspective. *Acta Obstet Gynecol Scand*. 2015 Jun;94(6):563-7. Epub 2015 Mar 29. PMID: 25721104.

Case 7:16-cv-00108-0 Document 26 Filed 10/21/16 Page 728 of 919 PageID 1194
T'Sjoen G, Weyers S, Taes Y, Lapaauw S, Roeyt, Goemaere S, Kaufman. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. *J Clin Densitom.* 2009 Jul-Sep;12(3):306-13. Epub 2009 Jan 3. PMID: 19121966.

T'Sjoen G, De Cuypere G, Monstrey S, Hoebeke P, Freedman F, Appari M, Holterhus P, Van Borsel J, Cools M. Male gender identity in complete androgen insensitivity syndrome. *Arch Sex Behav.* 2011 Jun;40(3):635-8. Epub 2010 Apr 1. PMID: 20358272.

TSjoen G, Van Caenegem E, Wierckx K. Transgenderism and reproduction. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):575-9. PMID: 24468761.

Tsoi WF, Kok LP, Long FY. Male transsexualism in Singapore: a description of 56 cases. *Br J Psychiatry.* 1977 Oct;131:405-9. PMID: 922268.

Tsoi WF. The prevalence of transsexualism in Singapore. *Acta Psychiatr Scand.* 1988 Oct;78(4):501-4. PMID: 3265846.

Tsoi WF. Male and female transsexuals: a comparison. *Singapore Med J.* 1992 Apr;33(2):182-5. PMID: 1621125.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J.* 1993 Dec;34(6):515-7. PMID: 8153713.

Tsoi WF, Kok LP, Yeo KL, Ratnam SS. Follow-up study of female transsexuals. *Ann Acad Med Singapore.* 1995 Sep;24(5):664-7. PMID: 8579306.

Tsushima WT, Wedding D. MMPI results of male candidates for transsexual surgery. *J Pers Assess.* 1979. Aug;43(4):385-7. PMID: 383946.

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. *Sexual and Relationship Therapy*. 2008 May; 23(2):141-5. (Not in PubMed)

Urban R, Teng N, Kapp D. Gynecologic malignancies in female-to-male transgender patients: the need of original gender surveillance. *Am J Obstet Gynecol*. 2011 May;204(5):e9-e12. Epub 2011 Feb 26. PMID: 21354550.

Vacchiano RB, Strauss PS. The construct validity of the Tennessee self concept scale. *J Clin Psychol*. 1968 Jul;24(3):323-6. PMID: 5661752.

Van Caenegem E, Wierckx K, Taes Y, Dedeker D, Van de Peer F, Toye K, Kaufman J, T'Sjoen G. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab*. 2012 Jul;97(7):2503-11. Epub 2012 May 7. PMID: 22564669.

A-Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman J, Schreiner T, Haraldsen I. T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone*. 2013 May;54(1):92-7. Epub 2013 Jan 28. PMID: 23369987.

B-Van Caenegem E, Verhaeghe E, Taes Y, Wierckx K, Toye K, Goemaere S, Zmierzak H, Hoebeke P, Monstrey S, T'Sjoen G. Long-term evaluation of donor-site morbidity after radial forearm flap phalloplasty for transsexual men. *J Sex Med*. 2013 Jun;10(6):1644-51. Epub 2013 Mar 27. PMID: 23534878.

Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman J, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol*. 2015 Feb;172(2):163-71. PMID: 25550352.

Van Caenegem E, Wierckx K, Elaut E, Buysse A, Dewaele A, Van Nieuwerburgh F, De Cuypere G, T'Sjoen G. Prevalence of Gender Nonconformity in Flanders, Belgium. *Arch Sex Behav*. 2015 Jul;44(5):1281-7. Epub 2015

VanderLaan DP, Vokey JR, Vasey PL. Is Transgendered Male Androphilia Familial in Non-Western Populations? The Case of a Samoan Village. *Arch Sex Behav*. 2013; 42:361-70. PMID: 23187702.

Van Kesteren PJ, Gooren LJ, Megens JA. An epidemiological and demographic study of transsexuals in The Netherlands. *Arch Sex Behav*. 1996 Dec;25(6):589-600. PMID: 8931882.

Van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997 Sep;47(3):337-42. PMID: 9373456.

Vasey PL, Bartlett NH. What can the Samoan "Fa'afafine" teach us about the Western concept of gender identity disorder in childhood? *Perspect Biol Med*. 2007 Autumn;50(4):481-90. PMID: 17951883.

Veatch RM. Indifference of subjects: An alternative to equipoise in randomized clinical trials. *Soc Phil Policy*. 2002; 19:295-323. PMID: 12678091.

Veale J. Prevalence of transsexualism among New Zealand passport holders. *Aust N Z J Psychiatry*. 2008 Oct;42(10):887-9. PMID: 18777233.

Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study. *J Adolesc Health*. 2015 Oct;57(4):367-73. Epub 2015 Jun 25. PMID: 26119518.

Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. *J Sex Med*. 2009 Apr;6(4):1018-23. Epub 2008 Mar 4. PMID: 18331254.

Vujović S, Popović S, Mrvošević Marojević L, Ivović M, Tančić-Gajić M, Stojanović M, Marina LV, Barać M, Barać B, Kovačević Case 3:16-cv-00108-D Document 26 Filed 10/21/16 Page 731 of 919 PageID 1197
Walinder J, Lundstrom B, Thuwe I. Prognostic factors in the assessment of male transsexuals for sex reassignment. *Scientific World Journal*. 2014 May 20;2014:Article 763563. 4 pages. PMID: 24982993.

Walinder J, Thuwe I. *A social-psychiatric follow- up study of 24 sex-reassigned transsexuals*. Gothenburg: Scandinavian University Books, Akademiforlaget. 1975.

Walinder J, Lundstrom B, Thuwe I. Prognostic factors in the assessment of male transsexuals for sex reassignment. *Br J Psychiatry*. 1978;132: 16-20. (Not in PubMed)

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992 Jun;30(6):473-83. PMID: 1593914.

Watson D, Friend R. Measurement of social-evaluative anxiety. *J Consult Clin Psychol*. 1969 Aug;33(4):448-57. PMID: 5810590.

Weigert R, Frison E, Sessieq Q, Al Mutairi K, Casoli V. Patient satisfaction with breasts and psychosocial, sexual, and physical well-being after breast augmentation in male-to-female transsexuals. *Plast Reconstr Surg*. 2013 Dec;132(6):1421-9. PMID: 24281571.

A-Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med*. 2009 Mar;6(3):752-60. Epub 2008 Nov 17. PMID: 19040622.

B-Weyers S, Decaestecker K, Verstraelen H, Monstrey S, T'Sjoen G, Gerris J, Hoebeke P, Villeirs G. Clinical and transvaginal sonographic evaluation of the prostate in transsexual women. *Urology*. 2009 Jul;74(1):191-6. Epub 2009 Apr 23. PMID: 19395005.

WHO 1996: Harper A. Manual for World Health Organization Quality of Life Abbreviated. Director Dr. J. Orley. http://www.who.int/mental_health/media/en/76.pdf.

WHO 2011: Carlos F. Caceres CF, GerbaseA, Ying-Ru Lo Y-R, Rodolph M (key drafters). *Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with other men and transgender people. Recommendations for a public health approach*. World Health Organization. 2011. http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/.

WHO 2014: Chris Beyrer C, Kamarulzaman A (co-chairs.) World Health Organization. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations*. July 2014. www.who.int/hiv/pub/guidelines/keypopulations/en/.

WHO 2015: Poteat T, Keatley J. (key drafters). *Policy Brief: Transgender People and HIV*. World Health Organization. July 2015. <http://www.who.int/hiv/pub/transgender/transgender-hiv-policy/en/>.

Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther*. 2005 Jan-Feb;31(1):1-20. PMID: 15841702.

A-Wierckx K, Elaut E, Van Caenegem E, Van De Peer F, Dedeker D, Van Houdenhove E, T'Sjoen G. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur J Endocrinol*. 2011 Aug;165(2):331-7. Epub 2011 May 20. PMID: 21602316.

B-Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011 Dec;8(12):3379-88. Epub 2011 Jun 23. PMID: 21699661.

A-Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedeker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. *Hum Reprod*. 2012 Feb;27(2):483-7. Epub 2011 Nov 28. PMID: 22128292.

B-Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. *J Sex Med*. 2012 Oct;9(10):2641-51. Epub 2012 Aug 20. PMID: 22906135.

Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, Kaufman J, T'Sjoen G. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol*. 2013 Oct;169(4):471-8. Epub 2013 Sep 13. PMID: 23904280.

A-Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med*. 2014 Jan;11(1):107-18. Epub 2013 Oct 24. PMID: 24165564.

B-Wierckx K, Gooren L, T'Sjoen G. Clinical review: Breast development in trans women receiving cross-sex hormones. *J Sex Med*. 2014 May;11(5):1240-7. Epub 2014 Mar 12. PMID: 24618412.

Williamson C. Providing care to transgender persons: a clinical approach to primary care, hormones, and HIV management. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):221-9. Epub 2010 Apr 3. PMID: 20363651.

Wilson CA, Davies DC. The control of sexual differentiation of the reproductive system and brain. *Reproduction*. 2007 Feb;133(2):331-59. PMID: 17307903.

Wilson EC, Garofalo R, Harris DR, Belzer M. Sexual risk taking among transgender male-to-female youths with different partner types. *Am J Public Health*. 2010 Aug;100(8):1500-5. Epub 2009 Nov 12. PMID: 20622176.

Wilson E, Pant SB, Comfort M, Ekstrand M. Stigma and HIV risk among Metis in Nepal. *Cult Health Sex*. 2011 Mar;13(3):253-66. PMID: 21058085.

Wilson P, Sharp C, Carr S. The prevalence of gender dysphoria in Scotland: a primary care study. *Brit J Gen Pract*. 1999; 49 (449): 991-2. PMID: 10824346.

Case 7:16-cv-00108-0 Document 26 Filed 10/21/16 Page 734 of 919 PageID 1200
Wilson RC, Winkler S, Dume L, Obeid J, Azar M, Najmabadi H, Saffari-New M. Ethnic-specific distribution of mutations in 716 patients with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. *Mol Genet Metab*. 2007 Apr;90(4):414-21. Epub 2007 Feb 1. Erratum in: *Mol Genet Metab*. 2008 Feb;93(2):219. Azar, Maryam [corrected to Azar, Maryam Razzaghy]. PMID: 17275379.

A-Wise LA, Palmer JR, Hatch EE, Troisi R, Titus-Ernstoff L, Herbst AL, Kaufman R, Noller KL, Hoover RN. Secondary sex ratio among women exposed to diethylstilbestrol in utero. *Environ Health Perspect*. 2007 Sep;115(9):1314-9. PMID: 17805421.

B-Wise LA, Titus-Ernstoff L, Palmer JR, Hoover RN, Hatch EE, Perez KM, Strohsnitter WC, Kaufman R, Anderson D, Troisi R. Time to pregnancy and secondary sex ratio in men exposed prenatally to diethylstilbestrol. *Am J Epidemiol*. 2007 Oct 1;166(7):765-74. Epub 2007 Jun 27. PMID: 17596265.

Wise TN, Meyer JK. The border area between transvestism and gender dysphoria: transvestitic applicants for sex reassignment. *Arch Sex Behav*. 1980 Aug;9(4):327-42. PMID: 7416946.

Wolfradt U, Engelmann S. Depersonalization, fantasies, and coping behavior in clinical context. *J Clin Psychol*. 1999 Feb;55(2):225-32. PMID: 10100823.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. *Arch Sex Behav*. 2001 Jun;30(3):301-10 PMID: 11330119.

WPATH 2001 Meyer III W, Bockting WO, Cohen-Kettenis P, Coleman E, DiCeglie D, Devor H, Gooren L, Hage JJ, Kirk S, Kuiper B., Laub D., Lawrence A., Menard Y., Monstrey S, Patton J, Schaefer L., Webb A, Wheeler CC .*The Harry Benjamin International Gender Dysphoria Association's Standards Of Care For Gender Identity Disorders*. (6th version) February, 2001.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=4655.

WPATH 2012 Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Istar Lev A, Mayer G, Meyer-Bahlburg H, Paxton Hall B, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. *Standards of care for the health of transsexual, transgender, and gender-nonconforming people*. (7th version) 2012.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926

Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):570-4. PMID: 24468760.

Wyler J, Battegay R, Krupp S, Rist M, Rauchfleisch U. [Transsexualism and its therapy]. *Schweiz Arch Neurol Neurochir Psychiatr.* 1979;124(1):43-58. PMID: 482895.

Yahyaoui R, Esteva I, Haro-Mora J, Almaraz M, Morcillo S, Rojo-Martínez G, Martínez J, Gómez-Zumaquero J, González I, Hernando V, Soriguer F. Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab.* 2008 Jun;93(6):2230-3. Epub 2008 Mar 18. PMID: 18349066.

Yik Koon, T. (2002). *The Mak Nyahs: Malaysian Male to Female Transsexuals.* (Chapter 4) Eastern Universities Press.

Zhu, Y, Imperato-McGinley, J, Male Sexual Differentiation Disorder and 5 α -Reductase-2 Deficiency. *Glob. libr. women's med.*, (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10350. (Not in PubMed.)

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983 Jun;67(6):361-70. PMID: 6880820.

Zimmermann A, Zimmer R, Kovacs L, Einödshofer S, Herschbach P, Henrich G, Tunner W, Biemer E, Papadopoulos N. [Transsexuals' life satisfaction after gender transformation operations]. *Chirurg.* 2006 May;77(5):432-8. German. Erratum in *Chirurg.* 2006 Jun;77(6):530. PMID: 16437228.

Zoni AC, González MA, Sjögren HW. Syphilis in the most at-risk populations in Latin America and the Caribbean: a systematic review. *Int J Infect Dis.* 2013 Feb;17(2):e84-92. Epub 2012 Oct 12. PMID: 23063547.

A-Zucker KJ, Bradley SJ, Kuksis M, Pecore K, Birkenfeld-Adams A, Doering RW, Mitchell JN, Wild J. Gender constancy judgments in children with gender identity disorder: evidence for a developmental lag. *Arch Sex Behav*. 1999 Dec;28(6):475-502. PMID: 10650437.

B-Zucker KJ. Intersexuality and gender identity differentiation. *Annu Rev Sex Res*. 1999;10:1-69. PMID: 10895247.

Zucker K, Cohen-Kettenis P, Drescher J, Meyer-Bahlburg H, Pfäfflin F, Womack W. Memo outlining evidence for change for gender identity disorder in the DSM-5. *Arch Sex Behav*. 2013 Jul;42(5):901-14. PMID: 23868018.

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Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N)

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Decision Summary

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination of whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery is reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination related to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

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Subject: Final Decision Memorandum on Gender Reassignment Surgery for Medicare Beneficiaries with Gender Dysphoria

Date: August 30, 2016

I. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

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II. Background

Below is a list of acronyms used throughout this document.

AHRQ - Agency for Healthcare Research and Quality
AIDS - Acquired Immune Deficiency Syndrome
ANOVA - Analysis of Variance
APA - American Psychiatric Association
APGAR - Adaptability, Partnership Growth, Affection, and Resolve test
BIQ - Body Image Questionnaire
BSRI - Bem Sex Role Inventory
CCEI - Crown Craps Experimental Index
CDC - Centers for Disease Control
CHIS - California Health Interview Survey
CI - Confidence Interval
CMS - Centers for Medicare & Medicaid Services
DAB - Departmental Appeals Board
DSM - Diagnostic and Statistical Manual of Mental Disorders
EMBASE - Excerpta Medica dataBASE
FBeK - Fragebogen zur Beurteilung des eigenen Körpers
FDA - Food and Drug Administration
FPI-R - Freiburg Personality Inventory
FSFI - Female Sexual Function Index
GAF - Global Assessment of Functioning
GID - Gender Identity Disorder
GIS - Gender Identity Trait Scale
GRS - Gender Reassignment Surgery
GSI - Global Severity Indices
HADS - Hospital Anxiety Depression Scale
HHS - U.S. Department of Health and Human Services
HIV - Human Immunodeficiency Virus
IIP - Inventory of Interpersonal Problems
IOM - Institute of Medicine
KHQ - King's Health Questionnaire
LGB - Lesbian, Gay, and Bisexual
LGBT - Lesbian, Gay, Bisexual, and Transgender
MAC - Medicare Administrative Contractor
MMPI - Minnesota Multiphasic Personality Inventory
NCA - National Coverage Analysis
NCD - National Coverage Determination
NICE - National Institute for Health Care Excellence
NIH - National Institutes of Health
NZHTA - New Zealand Health Technology Assessment
PIT - Psychological Integration of Trans-sexuals
QOL - Quality of Life
S.D. - Standard Deviation
SADS - Social Anxiety Depression Scale
SCL-90R - Symptom Check List 90-Revised
SDPE - Scale for Depersonalization Experiences
SES - Self Esteem Scale

A. Diagnostic Criteria

The criteria for gender dysphoria or spectrum of related conditions as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has changed over time (See Appendix A).

Gender dysphoria (previously known as gender identity disorder) is a classification used to describe persons who experience significant discontent with their biological sex and/or gender assigned at birth. Although there are other therapeutic options for gender dysphoria, consistent with the NCA request, this decision only focuses on gender reassignment surgery.

B. Prevalence of Transgender Individuals

For estimates of transgender individuals in the U.S., we looked at several studies.

The Massachusetts Behavior Risk Factor Surveillance Survey (via telephone) (2007 and 2009) identified 0.5% individuals as transgender (Conron et al., 2012).

Derivative data obtained from the 2004 California Lesbian Gay Bisexual and Transgender (LGBT) Tobacco Survey (via telephone) and the 2009 California Health Interview Survey (CHIS) (via telephone) suggested the LGB population constitutes 3.2% of the California population and that transgender subjects constitute approximately 2% of the California LGBT population and 0.06% of the overall California population (Bye et al., 2005; CHIS 2009; Gates, 2011).

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Most recently, the Williams Institute published a report that utilized data from the Centers for Disease Control's (CDC) Behavioral Risk Factor Surveillance System (BRFSS). Overall, they found that 0.6% or 1.4 million U.S. adults identify as transgender. The report further estimated 0.7% of adults between the ages of 18-25 identify as transgender, 0.6% of adults between the ages of 25-65 identify as transgender, and 0.5% of adults age 65 or older identify as transgender (Flores et al., 2016).

In a recent review of Medicare claims data, CMS estimated that in calendar year 2013 there were at least 4,098 transgender beneficiaries (less than 1% of the Medicare population) who utilized services paid for by Medicare, of which 90% had confirmatory diagnosis, billing codes, or evidence of a hormone therapy prescription. The Medicare transgender population is racially and ethnically diverse (e.g., 74% White, 15% African American) and spans the entire country. Nearly 80% of transgender beneficiaries are under age 65, including approximately 23% ages 45-54. (CMS Office of Minority Health 2015).

For international comparison purposes, recent estimates of transgender populations in other countries are similar to those in the United States. New Zealand researchers, using passport data, reported a prevalence of 0.0275% for male-to-female adults and 0.0044% female-to-male adults (6:1 ratio) (Veale, 2008). Researchers from a centers of transgender treatment and reassignment surgery in Belgium conducted a survey of regional plastic surgeons and reported a prevalence of 0.008% male-to-female and 0.003% female-to-male (ratio 2.7:1) surgically reassigned transsexuals in Belgium (De Cuypere et al., 2007). Swedish researchers, using national mandatory reporting data on those requesting reassignment surgery, reported secular changes over time in that the number of completed reassignment surgeries per application increased markedly in the 1990s; the male-to-female/female-to-male sex ratio changed from 1:1 to 2:1; the age of male-to-female and female-to-male applicants was initially similar, but increased by eight years for male-to-female applicants; and the proportion of foreign born applicants increased (Olsson and Moller 2003).

III. History of Medicare Coverage

Date	Action
August 1, 1989	CMS published the initial NCD, titled "140.3, Transsexual Surgery" in the Federal Register. (54 Fed. Reg. 34,555, 34,572)
May 30, 2014	The HHS Departmental Appeals Board (DAB) determined that the NCD denying coverage for all transsexual surgery was not valid. As a result, MACs determined coverage on a case-by-case basis.

CMS does not currently have a NCD on gender reassignment surgery.

A. Current Request

On December 3, 2015, CMS accepted a formal complete request from a beneficiary to initiate a NCA for gender reassignment surgery.

CMS opened this National Coverage Analysis (NCA) to thoroughly review the evidence to determine whether or not gender reassignment surgery may be covered nationally under the Medicare program.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For gender reassignment surgery, the following are statutes are applicable to coverage:

Under §1812 (Scope of Part A) Under §1832 (Scope of Part B)
 Under §1861(s) (Definition of Medical and Other Health Services)
 Under §1861(s)(1) (Physicians' Services)

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Timeline of Medicare Coverage Policy Actions for Gender Reassignment Surgery

Date	Action
December 3, 2015	CMS accepts an external request to open a NCD. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
January 2, 2016	Initial comment period closed. CMS received 103 comments.
June 2, 2016	Proposed Decision Memorandum posted on the web site and the final 30 day public comment period commenced.
July 2, 2016	Final comment period closed. CMS received 45 comments.

V. FDA Status

Surgical procedures per se are not subject to the Food and Drug Administration's (FDA) approval.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical question relevant to the coverage request can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer-reviewed medical journals. We also considered articles cited by the requestor, articles identified in public comments, as well as those found by a CMS literature review. Citations are detailed below.

B. Literature Search Methods

The reviewed evidence included articles obtained by searching literature databases and technology review databases from PubMed (1965 to current date), EMBASE, the Agency for Healthcare Research and Quality (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies. Systematic reviews were used to help locate some of the more obscure publications and abstracts.

Keywords used in the search included: Trans-sexual, transgender, gender identity disorder (syndrome), gender dysphoria and/or hormone therapy, gender surgery, genital surgery, gender reassignment (surgery), sex reassignment (surgery) and/or quality of life, satisfaction-regret, psychological function (diagnosis of mood disorders, psychopathology, personality disorders), suicide (attempts), mortality, and adverse events-reoperations. After the identification of germane publications, CMS also conducted searches on the specific psychometric instruments used by investigators.

Psychometric instruments are scientific tools used to measure individuals' mental capabilities and behavioral style. They are usually in the form of questionnaires that numerically capture responses. These tools are used to create a psychological profile that can address questions about a person's knowledge, abilities, attitudes and personality traits. In the evaluation of patients with gender dysphoria, it is important that both validity and reliability be assured in the construction of the tool (validity refers to how well the tool actually measures what it was designed to measure, or how well it reflects the reality it claims to represent, while reliability refers to how accurately results of the tool would be replicated in a second identical piece of research). Reliability and validity are important because when evaluating patients with gender dysphoria most of the variables of interest (e.g., satisfaction, anxiety, depression) are latent in nature (not directly observed but are rather inferred) and difficult to quantify objectively.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than small, pilot studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important. Studies with fewer than 30 patients were reviewed and delineated, but excluded from the major analytic framework. Oral presentations, unpublished white papers, and case reports were excluded. Publications in languages other than English were excluded. The CMS initial internal search for the proposed decision memorandum was limited to articles published prior to March 21, 2016. The CMS internal search for the final decision memorandum continued through articles published prior to July 22, 2016.

Included studies were limited to those with adult subjects. Review and discussion of the management of children and adolescents with the additional considerations of induced pubertal delay are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. The excluded duplicative publications are delineated.

C. Discussion of Evidence

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" For this specific NCA, CMS is interested in answering the following question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

The evidence reviewed is directed towards answering this question.

1. Internal Technology Assessment

CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions.

CMS identified numerous publications related to gender reassignment surgery. A large number of these were case reports, case series with or without descriptive statistics, or studies with population sizes too small to conduct standard parametric statistical analyses. Others addressed issues of surgical technique.

CMS identified and described 36 publications on gender reassignment surgery that included health outcomes. Because the various investigators at a site sometimes conducted serial studies on ever-enlarging cohort populations, studied sub-populations, studied different outcomes, or used different tools to study the same outcomes, not all study populations were unique. To reduce bias from over-lapping populations, only the latest or most germane publication(s) were described. Subsumed publications were delineated.

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Of these 36 publications, two publications used different assessment tools on the same population, and, so for the purposes of evaluation, were classified as one study (Udeze et al., 2008; Megeri and Khoosal, 2007). A total of 33 studies were reviewed (See Figure 1). Appendices C, D, and F include more detail of each study. The publications covered a time span from 1979 to 2015. Over half of the studies were published after 2005.

Figure 1. Studies of Gender Reassignment Surgery (GRS)



ANOVA=Analysis of Variance Normative=Psychometric Tests with known normative for large populations

Figure 1 Legend: The studies in Figure 1 are categorized into three groups. The first group, depicted by the colored boxes (red, blue, and green), had explicit controls. There was a single randomized study. The remainder in the first group were observational studies. These were subdivided into longitudinal studies and cross-sectional studies. The second group, depicted by black boxes (starting with the surgery only population box) consisted of surgical series. The third group, depicted by black boxes (starting with mixed population), was composed of patients whose treatment could involve a variety of therapeutic interventions, but who were not stratified by that treatment.

When looking at the totality of studies, the 33 studies could be characterized by the following research design groups:

a. Observational, mixed population of surgical and non-surgical patients without stratification

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011 Apr;164(4):635-42. Epub 2011 Jan 25.

Asscheman et al. conducted a retrospective, non-blinded, observational study of mortality using a longitudinal design to assess a mixed population treated with hormones, as well as, reassignment surgery in comparison to a population-based cohort. The study was not designed to assess the specific impact of gender reassignment surgery on clinical outcomes.

The investigators assessed mortality in patients who (a) were from a single-center, unspecified, Dutch university specialty clinic, (b) had initiated cross-sex hormone treatment prior to July 1, 1997, and (c) had been followed (with or without continued hormone treatment) by the clinic for at least one year or had expired during the first year of treatment. The National Civil Record Registry (Gemeentelijke Basis Administratie) was used to identify/confirm deaths of clinic patients. Information on the types or hormones used was extracted from clinic records, and information on the causation of death was extracted from medical records or obtained from family physicians. Mortality data for the general population were obtained through the Central Bureau of Statistics of the Netherlands (Centraal Bureau voor de Statistiek). Mortality data from Acquired Immune Deficiency Syndrome (AIDS) and substance abuse were extracted from selected Statistics Netherlands reports. The gender of the general Dutch population comparator group was the natal sex of the respective gender dysphoric patient groups.

A total of 1,331 patients who met the hormone treatment requirements were identified (365 female-to-male [27.4%]; 966 male-to-female [72.6%]; ratio 1:2.6). Of these, 1,177 (88.4%) underwent reassignment surgery (343 [94.0% of female-to-male entrants]; 834 [86.3% of male-to-female entrants]; ratio difference 1:2.4 with a p-value $p < 0.0001$). Later calculations did not distinguish between those with hormone therapy alone versus those with hormone therapy plus reassignment surgery. The mean age at the time of hormone initiation in female-to-male and male-to-female patients was 26.1 ± 7.6 (range 16–56) years and 31.4 ± 11.4 (range 16–76) years respectively, although the male-to-female subjects were relatively older ($p < 0.001$). The mean duration of hormone therapy in female-to-male and male-to-female patients was 18.8 ± 6.3 and 19.4 ± 7.7 years respectively.

There were a total of 134 deaths in the clinic population using hormone therapy with or without surgical reassignment. Of these patients, 12 (3.3%) of the 365 female-to-male patients and 122 (12.6%) of the 966 male-to-female patients died. All-cause mortality for this mixed population was 51% higher and statistically significant (Standardized Mortality Ratio [SMR] 95% confidence interval [CI] 1.47–1.55) for males-to-females when compared to males in the general Dutch population. The increase in all-cause mortality (12%) for females-to-males when compared to females in the general Dutch population was not statistically significant (95% CI 0.87–1.42).

Ischemic heart disease was a major disparate contributor to excess mortality in male-to-female patients but only in older patients ($n=18$, SMR 1.64 [95% CI 1.43–1.87]), mean age [range]: 59.7 [42–79] years. Current use of a particular type of estrogen, ethinyl estradiol, was found to contribute to death from myocardial infarction or stroke (Adjusted Hazard Ratio 3.12 [95% CI 1.28–7.63], $p=0.01$). There was a small, but statistically significant increase in lung cancer that was thought to possibly be related to higher rates of smoking in this cohort.

Other contributors to the mortality difference between male-to-female patients and the Dutch population at large were completed suicide ($n=17$, SMR 5.70 [95% CI 4.93–6.54]), AIDS ($n=16$, SMR 30.20 [95% CI 26.0–34.7]), and illicit drug use ($n=5$, SMR 13.20 [95% CI 9.70–17.6]). An additional major contributor was “unknown cause” ($n=21$, SMR 4.00 [95% CI 3.52–4.51]). Of the 17 male-to-female hormone treated patients who committed suicide, 13 (76.5%) had received prior psychiatric treatment and six (35.3%) had not undergone reassignment surgery because of concerns about mental health stability.

This study subsumes earlier publications on mortality (Asscheman et al. 1989 [n=425]; Van Kesteren et al. 1997 [n=816]).

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone- treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012 May;37(5):662-70. Epub 2011 Sep 19.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a cross-sectional design and non-specific psychiatric distress tools in Spain. The investigators assessed anxiety and depression in patients with gender dysphoria who attended a single-center specialty clinic with comprehensive endocrine, psychological, psychiatric, and surgical care. The clinic employed World Professional Association for Transgender Health (WPATH) guidelines. Patients were required to have met diagnostic criteria during evaluations by 2 experts. Investigators used the Hospital Anxiety and Depression Scale (HADS) and the Social Anxiety and Distress Scale (SADS) instruments. The SADS total score ranges from 0 to 28, with higher scores indicative of more anxiety. English language normative values are 9.1 ± 8.0 . HAD-anxiety and HAD-depression total score ranges from 0 to 21, with higher scores indicative of more pathology. Scores less than 8 are normal. ANOVA was used to explore effects of hormone and surgical treatment.

Of the 200 consecutively selected patients recruited, 187 (93.5% of recruited) were included in the final study population. Of the final study population, 74 (39.6%) were female-to-male patients; 113 (60.4%) were male-to-female patients (ratio 1:1.5); and 120 (64.2%) were using hormones. Of those using hormones, 36 (30.0%) were female-to-male; 84 (70.0%) were male-to-female (ratio 1:2.3). The mean age was 29.87 ± 9.15 years (range 15-61). The current age of patients using hormones was 33.6 ± 9.1 years (n=120) and older than the age of patients without hormone treatment (25.9 ± 7.5) ($p=0.001$). The age at hormone initiation, however, was 24.6 ± 8.1 years.

Of those who had undergone reassignment surgery, 29 (36.7%) were female-to-male; 50 (63.3%) were male-to-female (ratio 1:1.7). The number of patients not on hormones and who had undergone at least one gender-related surgical procedure (genital or non-genital) was small (n=2). The number of female-to-male patients on hormones who had undergone such surgery (mastectomy, hysterectomy, and/or phalloplasty) was 28 (77.8%). The number of male-to-female patients on hormones who had undergone such surgery (mammoplasty, facial feminization, buttock feminization, vaginoplasty, orchiectomy, and/or vocal feminization (thyroid chondroplasty) was 49 (58.3%).

Analysis of the data revealed that although the mean scores HAD-Anxiety, HAD-Depression, and SADS were statistically lower (better) in those on hormone therapy than in those not on hormone therapy, the mean scores for HAD-Depression and SADS were in the normal range for gender dysphoric patients not using hormones. The HAD-Anxiety score was 9 in transsexuals without hormone treatment and 6.4 in transsexuals with hormone treatment.

treatment. The mean scores for HAD-Anxiety, HAD- Depression, and SADS were in the normal range for gender dysphoric patients using hormone. Document 26 Filed 10/21/16 Page 749 of 919 PageID 1215
Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-76. Epub 2013 Aug 13.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-76. Epub 2013 Aug 13.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a non-specific quality of life tool. There were no formal controls for this mixed population ± non-genital reassignment surgery undergoing various stages of treatment.

The investigators assessed quality of life in the context of culture in patients with gender dysphoria who were from a single-center (Barcelona, Spain), specialty and gender identity clinic. The clinic used WPATH guidelines. Patients were required to have met diagnostic criteria during evaluations by both a psychologist and psychiatrist. Patients could have undergone non-genital surgeries, but not genital reassignment surgeries (e.g., orchiectomy, vaginoplasty, or phalloplasty). The Spanish version of the World Health Organization Quality of Life-Abbreviated version of the WHOQOL-100 (WHOQOL- BREF) was used to evaluate quality of life, which has 4 domains (environmental, physical, psychological, and social) and 2 general questions. Family dynamics were assessed with the Spanish version of the Family Adaptability, Partnership Growth, Affection, and Resolve (APGAR) test. Regression analysis was used to explore effects of surgical treatment.

All consecutive patients presenting at the clinic (277) were recruited and, 260 (93.9%) agreed to participate. Of this number, 59 of these were excluded for incomplete questionnaires, 8 were excluded for prior genital reassignment surgery, and 193 were included in the study (the mean age of this group was 31.2±9.9 years (range 16-67). Of these, 74 (38.3%) were female-to-male patients; 119 (61.7%) were male-to-female patients (ratio1:1.6). Of these, 120 (62.2%) were on hormone therapy; 29 (39.2%) of female-to-male patients had undergone at least 1 non-genital, surgical procedure (hysterectomy n=19 (25.7%); mastectomy n=29 (39.2%)); 51 (42.9%) of male-to-female patients had undergone at least one non-genital surgical procedure with mammoplasty augmentation being the most common procedure, n=47 (39.5%), followed by facial feminization, n=11 (9.2%), buttocks feminization, n=9 (7.6%), and vocal feminization (thyroid chondroplasty), n=2 (1.7%).

WHOQOL-BREF domain scores for gender dysphoric patients with and without non-genital surgery were: "Environmental" 58.81±14.89 (range 12.50-96.88), "Physical" 63.51±17.79 (range 14.29-100), "Psychological" 56.09±16.27 (range 16.67- 56.09), "Social" 60.35±21.88 (range 8.33-100), and "Global QOL and Health" 55.44±27.18 (range 0-100 with higher score representing better QOL). The mean APGAR family score was 7.23±2.86 (range 0-10 with a score of 7 or greater indicative of family functionality).

Regression analysis, which was used to assess the relative importance of various factors to WHOQOL-BREF domains and general questions, revealed that family support was an important element for all four domains. Appendix 745

the general health and quality-of-life questions. Hormone therapy was an important element for the general questions and for the clinical diagnosis. Current and lifetime diagnosis of Axis 1 disorders, current and lifetime surgery, age, educational levels, and partnership status, did not impact domain and general question results related to quality of life.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005 Mar;58(3):259-61.

Hepp et al. conducted a single-site (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design. There was some acquisition of retrospective data. The investigators assessed current and lifetime psychiatry co-morbidity using structured interviews for diagnosis of Axis 1 disorders (clinical syndromes) and Axis 2 disorders (developmental or personality disorders) and HADS for dimensional evaluation of anxiety and depression. Statistical description of the cohort and intra-group comparisons was performed. Continuous variables were compared using t-tests and ANOVA.

A total of 31 patients with gender dysphoria participated in the study: 11 (35.5%) female-to-male; 20 (64.5%) male-to-female (ratio 1:1.8). The overall mean age was 32.2 ± 10.3 years. Of the participants, seven had undergone reassignment surgery, 10 pre-surgical patients had been prescribed hormone therapy, and 14 pre-surgical patients had not been prescribed hormone therapy. Forty five and one half percent of female-to-male and 20% of male-to-female patients did not carry a lifetime diagnosis of an Axis 1 condition. Sixty three and six tenths percent of female-to-male and 60% of male-to-female patients did not carry a current diagnosis of an Axis 1 condition. Lifetime diagnosis of substance abuse and mood disorder were more common in male-to-female patients (50% and 55% respectively) than female-to-male patients (36.4% and 27.3% respectively). Current diagnosis of substance abuse and mood disorder were present in male-to-female patients (15% and 20% respectively) and absent in female-to-male patients. One or more personality disorders were identified 41.9%, but whether this was a current or lifetime condition was not specified. Of the patients, five (16.1%) had a Cluster A personality disorder (paranoid-schizoid), seven (22.6%) had a Cluster B personality disorder (borderline, anti-social, histrionic, narcissistic), six (19.4%) had a Cluster C personality disorder (avoidant, dependent, obsessive-compulsive), and two (6.5%) were not otherwise classified.

HADS scores were missing for at least one person. The HADS test revealed non-pathologic results for depression (female-to-male: 6.64 ± 5.03 ; male-to-female: 6.58 ± 4.21) and borderline results for anxiety (female-to-male: 7.09 ± 5.11 ; male-to-female: 7.74 ± 6.13 , where a result of 7-10 = possible disorder). There were no differences by natal gender. The investigators reported a trend for less anxiety and depression as measured by HADS in the patients who had undergone surgery.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav. 2010 Dec;39(6):1429-37. Epub 2009 Oct 9.

Johansson et al. conducted a two center (Lund and Umeå, Sweden) non-blinded, observational study.

The investigators assessed satisfaction with the reassignment process, employment, partnership, sexual function, mental health, and global satisfaction in gender-reassigned persons from two disparate geographic regions. Surgical candidates were required to have met National Board of Health and Welfare criteria including initial and periodic psychiatric assessment, ≥ 1 year of real-life experience in preferred gender, and ≥ 1 year of subsequent hormone treatment. In addition, participants were required to have been approved for reassignment five or more years prior and/or to have completed surgical reassignment (e.g., sterilization, genital surgery) two or more years prior. The investigators employed semi-structured interviews covering a self-designed list of 55 pre-formulated questions with a three or five point ordinal scale. Clinician assessment of Global Assessment of Functioning (GAF; Axis V) was also conducted and compared to initial finding during the study. Changes or differences considered to be biologically significant were not pre-specified except for GAF, which pre-specified a difference to mean change ≥ 5 points. Statistical corrections for multiple comparisons were not included. There was no stratification by treatment.

Of the pool of 60 eligible patients, 42 (70.0% of eligible) (17 [40.5 %] female-to-male; 25 [59.5%] male-to-female; ratio 1:1.5) were available for follow-up. Of these, 32 (53.3% of eligible) (14 [43.8%] female-to-male; 18 [56.2%] male-to-female [ratio 1:1.3]) had completed genital gender reassignment surgery (not including one post mastectomy), five were still in the process of completing surgery, and five (one female-to-male; four male-to-female; ratio 1:4) had discontinued the surgical process prior to castration and genital surgery.

The age (ranges) of the patients at entry into the program, reassignment surgery, and follow-up were 27.8 (18-46), 31.4 (22- 49), and 38.9 (28-53) years in the female-to-male group respectively and 37.3 (21-60), 38.2 (22-57), and 46.0 (25.0-69.0) years in the male- to-female group respectively. The differences in age by cohort group were statistically significant. Of participants, 88.2% of all enrolled female-to-male versus 44.0% of all enrolled female-to-male patients had cross-gender identification in childhood (versus during or after puberty) ($p < 0.01$).

Although 95.2% of all enrolled patients self-reported improvement in GAF, in contrast, clinicians determined GAF improved in 61.9% of patients. Clinicians observed improvement in 47% of female-to-male patients and 72% of male-to- female patients. A ≥ 5 point improvement in the GAF score was present in 18 (42.9%). Of note, three of the five patients who were in the process of reassignment and five of the five who had discontinued the process were rated by clinicians as having improved.

Of all enrolled 95.2% (with and without surgery) reported satisfaction with the reassignment process. Of these 42 patients, 33 (79%) identified themselves by their preferred gender and nine (21%) identified themselves as transgender. None of these nine (eight male-to-female) had completed reassignment surgery because of ambivalence secondary to lack of acceptance by others and dissatisfaction with their appearance. Of the patients who underwent genital surgery ($n=32$) and mastectomy only ($n=one$), 22 (66.7%) were satisfied while four (three female-to-male) were dissatisfied with the surgical treatment.

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Regarding Relationships and Surgery, 16 (38.1%) (41.2% of female- to-male; 36.0% of male-to-female patients) were reported to have a partner. Yet more than that number commented on partner relationships: (a) 62.2 % of the 37 who answered (50.0% of female- to- male; 69.6% of male-to-female patients) reported improved partner relationships (five [11.9%] declined to answer.); (b) 70.0% of the 40 who answered (75.0% of female-to-male; 66.7% of male-to-female patients) reported an improved sex life. Investigators observed that reported post-operative satisfaction with sex life was statistically more likely in those with early rather than late cross-gender identification. In addition 55.4% self-reported improved general health; 16.1% reported impaired general health; 11.9% were currently being treated with anti-depressants or tranquilizers.

This study subsumes earlier work by Bodlund et al. (1994, 1996). The nationwide mortality studies by Dhejne et al. (2011) may include all or part of this patient population.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. Endocr Pract. 2013 Jul-Aug;19(4):644-50. (United States study)

Leinung et al. conducted a single-center (Albany, New York) a partially prospective, non-blinded, observational study using a cross-sectional design and descriptive statistics. There were no formal controls. The investigators assessed employment, substance abuse, psychiatric disease, mood disorders, Human Immunodeficiency Virus (HIV) status in patients who had met WPATH guidelines for therapy, and who had initiated cross-sex hormone treatment.

A total of 242 patients treated for gender identity disorder in the clinic from 1992 through 2009 inclusive were identified. The number of those presenting for therapy almost tripled over time. Of these patients, 50 (20.7%) were female-to-male; 192 (79.3%) male-to-female (ratio 1:3.8).

The age of female-to-male and male-to-female patients with gender dysphoria at the time of clinic presentation was 29.0 and 38.0 years respectively.

The female-to-male and male-to-female patients with gender dysphoria at the time of hormone initiation were young: 27.5 and 35.5 years old respectively ($p < 0.5$). Of the male-to-female cohort, 19 (7.8%) had received hormone therapy in the absence of physician supervision; Of the patient population, 91 (37.6%) had undergone gender-reassignment surgery (32 female-to-male [64.0% of all female-to- male; 35.2% of all surgical patients]; 59 male-to-female [30.7% of all male-to-female; 64.8% of all surgical patients]; ratio 1:1.8).

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Psychiatric disease was more common in those who initiated hormone therapy at an older age (>32 years) 63.9% versus 39.4% at a younger age, but by natal gender (40.0% of female-to-male; 58.3% male-to-female). Mood disorders were more common in those who initiated hormone therapy at an older age (>32 years) 52.1% versus 36.0% at a younger age and this finding did not differ by natal gender (40.0% of female-to-male; 44.8% male-to-female). The presence of mood disorders increased the time to reassignment surgery in male-to-female patients.

Motmans J , Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. J Sex Med. 2012 Mar;9(3):743-50. Epub 2011 Dec 21.

Motmans et al., conducted a prospective, non-blinded, observational study using a cross-sectional design and a non-specific quality of life tool. No concurrent controls were used in this study. Quality of life in this Dutch-speaking population was assessed using the Dutch version of a SF-36 (normative data was used). Participants included subjects who were living in accordance with the preferred gender and who were from a single Belgian university specialty clinic at Ghent. The Dutch version of the SF-36 questionnaire along with its normative data were used. Variables explored included employment, pension status, ability to work, being involved in a relationship. Also explored, was surgical reassignment surgery and the types of surgical interventions. Intragroup comparisons by transgender category were conducted, and the relationships between variables were assessed by analysis of variance (ANOVA) and correlations.

The age of the entire cohort (n=140) was 39.89±10.21 years (female-to-male: 37.03±8.51; male-to-female: 42.26±10.39). Results of the analysis revealed that not all female-to-male patients underwent surgical reassignment surgery and, of those who did, not all underwent complete surgical reassignment. The numbers of female-to-male surgical interventions were: mastectomy 55, hysterectomy 55, metaoidplasty eight (with five of these later having phalloplasty), phalloplasty 40, and implantation of a prosthetic erectile device 20. The frequencies of various male-to-female surgical interventions were: vaginoplasty 48, breast augmentation 39, thyroid cartilage reduction 17, facial feminization 14, and hair transplantation three.

The final number of subjects with SF-36 scores was 103 (49 [47.6%] female-to-male; 54 [52.4%] male-to-female; ratio 1:1.1). For this measure, the scores for the vitality and mental health domains for the final female-to-male cohort (n= 49 and not limited to those having undergone some element of reassignment surgery) were statistically lower: 60.61±18.16 versus 71.9±18.31 and 71.51±16.40 versus 79.3±16.4 respectively. Scores were not different from the normative data for Dutch women: vitality: 64.3±19.7 or mental health 73.7±18.2. None of the domains of the SF-36 for the final male-to-female cohort (n=54 and not limited to those having undergone some element of reassignment surgery) were statistically different from the normative data for Dutch women.

Analysis of variance indicated that quality of life as measured by the SF-36 did not differ by whether female-to-male patients had undergone genital surgery (metaoidoplasty or phalloplasty) or not. Also, ANOVA indicated that quality of life as measured by the SF-36 did not differ by whether male-to-female patients had undergone either breast augmentation or genital surgery (vaginoplasty) or not.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. Qual Life Res. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. (United States study)

Newfield et al. conducted a prospective, observational internet self-report survey of unknown blinding status using a cross-sectional design and a non-specific quality of life tool in a mixed population with and without hormone therapy and/or reassignment surgery. There were no formal controls.

The investigators recruited natal female participants identifying as male using email, internet bulletin boards, and flyers/postcards distributed in the San Francisco Bay Area. Reduction of duplicate entries by the same participant was limited to the use of a unique user name and password.

The investigators employed the Short-Form 36 (SF-36) Version 2 using U.S. normative data. They reported using both male and female normative data for the comparator SF-36 cohort. Data for the eight domains were expressed as normative scoring. The Bonferroni correction was used to adjust for the risk of a Type 1 error with analyses using multiple comparisons.

A total of 379 U.S. respondents classified themselves as males-or-females to males with or without therapeutic intervention. The mean age of the respondents who classified themselves as male or female-to-male was 32.6 ± 10.8 years. Of these 89% were Caucasian, 3.6% Latino, 1.8% African American, 1.8% Asian, and 3.8% other. Of these, 254 (67.0%) reported prior or current testosterone use while 242 (63.8%) reported current testosterone use. In addition, 136 (36.7%) reported having had "top" surgery and 11 (2.9%) reported having "bottom" surgery.

Complete SF-36 data were available for 376 U.S. respondents. For the complete, non-stratified U.S. cohort the Physical Summary Score (53.45 ± 9.42) was statistically higher (better) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was within one standard deviation of the normative mean. The Mental Summary Score (39.63 ± 12.2) was statistically lower (worse) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was well within two standard deviations of the normative mean. Subcomponents of this score: Mental Health (42.12 ± 10.2), Role Emotional (42.42 ± 11.6), Social Functioning (43.14 ± 10.9), and Vitality (46.22 ± 9.9) were statistically lower (worse) than the SF-36 normative sub-scores, but well within one standard deviation of the normative sub-score means. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

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Additional intragroup analyses were conducted, although the data were not stratified by type of therapeutic intervention (hormonal, surgical, or both). Outcomes of interest were considered separately and dichotomously from reassignment surgery. The Mental Summary Score was statistically higher (better) in those who had "Ever Received Testosterone" (41.22 ± 11.9) than those with "No Testosterone Usage" (36.08 ± 12.6) ($p=0.001$). The Mental Summary Scores showed a trend towards statistical difference between those who "Ever Received Top Surgery" (41.21 ± 11.6) and those without "Top Surgery" (38.01 ± 12.5) ($p=0.067$). These differences were well within one standard deviation of the normative mean. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

b. Observational, surgical series, without concurrent controls

Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. J Consult Clin Psychol. 1985 Jun; 53(3):295-304.

Blanchard et al. conducted a single-center (Ontario, Canada), prospective, non-blinded, cross-sectional study using a self-designed questionnaire and a non-specific psychological symptom assessment with normative data. The investigators assessed social adjustment and psychopathology in patients with gender dysphoria and who were at least one year post gender reassignment surgery. Reassignment surgery was defined as either vaginoplasty or mastectomy/construction of male chest contour with or without nipple transplants, but did not preclude additional procedures. Partner preference was determined using Blanchard's Modified Androphilia-Gynephilia Index, and the nature and extent of any psychopathology was determined with the Symptom Check List 90-Revised (SCL-90R). Differences in test scores considered to be biologically significant were not pre-specified in the methods.

Of the 294 patients (111 natal females and 183 natal males, ratio: 1:1.65) initially evaluated, 263 were diagnosed with gender dysphoria. Of these 79 patients participated in the study (38 female-to-male; 32 male-to-female with male partner preference; 9 male-to-female with female partner preference). The respective mean ages for these 3 groups were 32.6, 33.2, and 47.7 years with the last group being older statistically ($p=0.01$).

Additional surgical procedures in female-to-male patients included: oophorectomy/hysterectomy (92.1%) and phalloplasty (7.9%). Additional surgical procedures in male-to-female patients with male partner preference included facial hair electrolysis 62.5% and breast implantation (53.1%). Additional procedures in male-to-female patients with female partner preference included facial hair electrolysis (100%) and breast implantation (33.3%). The time between reassignment surgery and questionnaire completion did not differ by group.

Psychopathology as measured by the Global Severity Index of the SCL-90R was absent in all three patient groups. Interpretation did not differ by the sex of the normative cohort.

Of participants, 93.7% reported that they would definitely undergo reassignment surgery again. The remaining 6.3% (one female-to-male; one male-to-female with male partner preference; three male-to-female with female partner preference) indicated that they probably would undertake the surgery again. Post hoc analysis suggested that the more ambivalent responders had more recently undergone surgery. Of responders, 98.7% indicated that they preferred life in the reassigned gender. The one ambivalent subject was a skilled and well compensated tradesperson who was unable to return to work in her male dominated occupation.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg. 1997 Mar;31(1):39-45.

Eldh et al. conducted a non-blinded, observational study using a prospective cross-sectional design with an investigator designed questionnaire and retrospective acquisition of pre-operative data. The investigators assessed economic circumstances, family status, satisfaction with surgical results, and sexual function in patients who had undergone gender reassignment surgery.

Of the 175 patients who underwent reassignment surgery in Sweden, 90 responded. Of this number, 50 were female-to-male and 40 were male-to-female (ratio: 1:0.8). Patients reportedly were generally satisfied with the appearance of the reconstructed genitalia (no numbers provided). Of the patients who had undergone surgery prior to 1986, seven (14%) were dissatisfied with shape or size of the neo-phallus; eight (16%) declined comment. There were 14 (35%), with 12 having surgery prior to 1986 and two between 1986 and 1995 inclusive, were moderately satisfied because of insufficient vaginal volume; 8 (20%) declined comment. A neo-clitoris was not constructed until the later surgical cohort. Three of 33 reported no sensation or no sexual sensation. Eight had difficulties comprehending the question and did not respond.

A total of nine (18%) patients had doubts about their sexual orientation; 13 (26%) declined to answer the question. The study found that two female-to- male patients and two male-to-female patients regretted their reassignment surgery and continued to live as the natal gender, and two patients attempted suicide.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. Dtsch Arztebl Int. 2014 Nov 21;111(47):795-801.

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Hess et al. conducted a prospective, blinded, observational study using a cross-sectional design and a self-designed anonymous questionnaire. The investigators assessed pre/post-operative satisfaction in 224 female patients with gender dysphoria who were followed in a urology specialty clinic (Essen, Germany). Patients had met the ICD-10 diagnostic criteria, undergone gender reassignment surgeries including penile inversion vaginoplasty, and a Likert-style questionnaire with 11 elements. Descriptive statistics were provided.

There were 254 consecutive eligible patients who had undergone surgery between 2004 and 2010 identified and sent surveys, of whom 119 (46.9%) responded anonymously. Of the participants, 13 (10.9%) reported dissatisfaction with outward appearance and 16 (13.4%) did not respond; three (2.5%) reported dissatisfaction with surgical aesthetics and 25 (21.0%) did not respond; eight (6.7%) reported dissatisfaction with functional outcomes of the surgery and 26 (21.8%) did not respond; 16 (13.4%) reported they could not achieve orgasm and 28 (23.5%) did not respond; four (3.4%) reported feeling completely male/more male than female and 28 (23.5%) did not respond; six (5.0%) reported not feeling accepted as a woman, two (1.7%) did not understand the question, and 17 (14.3%) did not respond; and 16 (13.4%) reported that life was harder and 24 (20.2%) did not respond.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. (United States study)

Lawrence conducted a prospective, blinded observational study using a cross-sectional design and a partially self-designed quality of life tool using yes/no questions or Likert scales. The investigator assessed sexual function, urinary function, and other pre/post-operative complications in patients who underwent male-to-female gender reassignment surgery. Questions addressed core reassignment surgery (neo-vagina and sensate neo-clitoris) and related reassignment surgery (labiaplasty, urethral meatus revision, vaginal deepening/widening, and other procedures), use of electrolysis, and use of hormones.

Questionnaires were designed to be completed anonymously and mailed to 727 eligible patients. Of those eligible, 232 (32%) returned valid questionnaires. The age at the time reassignment surgery was 44 ± 9 (range 18-70) years and mean duration after surgery was 3 ± 1 (range 1-7) years.

Happiness with sexual function and the reassignment surgery was reported to be lower when permanent vaginal stenosis, clitoral necrosis, pain in the vagina or genitals, or other complications such as infection, bleeding, poor healing, other tissue loss, other tissue necrosis, urinary incontinence, and genital numbness were present. Quality of life was impaired when pain in the vagina or genitals was present.

Satisfaction with sexual function, gender reassignment surgery, and overall QOL was lower when genital sensation was impaired and when vaginal architecture and lubrication were perceived to be unsatisfactory. Intermittent regret regarding reassignment surgery was associated with vaginal hair and clitoral pain. Vaginal stenosis was associated with surgeries performed in the more distant past; whereas, more satisfaction with vaginal depth and width was present in more recent surgical treatment.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun; 66(4):371-2. PMID: 22624747.

Salvador et al. conducted a single center (Port Alegre, Brazil) prospective, non-blinded, observational study using a cross-sectional design (albeit over an extended time interval) and a self-designed quality of life tool. The investigators assessed regret, sexual function, partnerships, and family relationships in patients who had undergone gender reassignment surgery at least 24 months prior.

Out of the 243 enrolled in the clinic over a 10 year interval, 82 underwent sex reassignment surgery. There were 69 participants with a minimum 2-year follow up, of whom 52 patients agreed to participate in the study. The age at follow-up was 36.3 ± 8.9 (range 15-58) years with the time to follow-up being 3.8 ± 1.7 (2-7) years. A total of 46 participants reported pleasurable neo-vaginal sex and post-surgical improvement in the quality of their sexual experience. The quality of sexual intercourse was rated as satisfactory to excellent, average, unsatisfactory, or not applicable in the absence of sexual contact by 84.6%, 9.6%, 1.9%, and 3.8% respectively. Of the participants, 78.8% reported greater ease in initiating and maintaining relationships; 65.4% reported having a partner; 67.3% reported increased frequency of intercourse; 36.8% reported improved familial relationships. No patient reported regret over reassignment surgery. The authors did not provide information about incomplete questionnaires.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J*. 1993 Dec; 34(6):515-7.

Tsoi conducted a single-center (Singapore) prospective, non-blinded, observational study using a cross-sectional design and a self-designed quality of life tool. The investigator assessed overall life satisfaction, employment, partner status, and sexual function in gender-reassigned persons who had undergone gender reassignment surgery between 1972 and 1988 inclusive and who were approximately 2 to 5 years post-surgery. Acceptance criteria for surgery included good physical health, good mental health, absence of heterosexual tendencies, willingness to undergo hormonal therapy for ≥ 6 months, and willingness to function in the life of the desired gender for ≥ 6 months. Tsoi also undertook retrospective identification of variables that could predict outcomes.

The size of the pool of available patients was not identified. Of the 81 participants, 36 (44.4%) were female-to-male and 45 (55.6%) were male-to-female (ratio 1:1.25).

The mean ages at the time of the initial visit and operation were: female-to-male 25.4 ± 4.4 (range 14-36) and 27.4 ± 4.0 ; (range 14-36); male-to-female 22.9 ± 4.6 (range 14-36) and 24.7 ± 4.3 (14-36) years respectively. Of all participants, 14.8% were under age 20 at the time of the initial visit. All were at least 20 at the time of gender reassignment surgery.

All participants reported dressing without difficulty in the reassigned gender; 95% of patients reported good or satisfactory adjustment in employment and income status; 72% reported good or satisfactory adjustment in relationships with partners. Although the quality of life tool was self-designed, 81% reported good or satisfactory adjustment to their new gender, and 63% reported good or acceptable satisfaction with sexual activity. Of the female-to-male patients, 39% reported good or acceptable satisfaction with sex organ function in comparison to 91% of male-to-female patients ($p < 0.001$). (The author reported that a fully functioning neo-phallus could not be constructed at the time.) The age of non-intercourse sexual activity was the only predictor of an improved outcome.

Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med.* 2009 Mar;6(3):752-60. Epub 2008 Nov 17.

Weyers et al. (2009) conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments including a non-specific quality of life tool and a semi-specific quality of life tool (using normative data) along with two self-designed tools.

The investigators assessed general quality of life, sexual function, and body image from the prior four weeks in Dutch-speaking male-to-female patients with gender dysphoria who attended a single-center (Ghent, Belgium), specialized, comprehensive care university clinic. Investigators used the Dutch version of the SF-36 and results were compared to normative data from Dutch women and U.S. women. The 19 items of the Dutch version of the Female Sexual Function Index (FSFI) were used to measure sexual desire, function, and satisfaction. A self-designed seven question visual analog scale (VAS) was used to measure satisfaction with gender related body traits and appearance perception by self and others. A self-designed survey measured a broad variety of questions regarding personal medical history, familial medical history, relationships, importance of sex, sexual orientation, gynecologic care, level of regret, and other health concerns. For this study, hormone levels were also obtained.

The study consisted of 50 (71.5% of the eligible recruits) participants. Analysis of the data revealed that the patient's average age was 43.1 ± 10.4 years, and all of the patients had vaginoplasty. This same population also had undergone additional feminization surgical procedures (breast augmentation 96.0%, facial feminization 36.0%, vocal cord surgery 40.0%, and cricoid cartilage reduction 30.0%). A total of two (4.0%) participants reported "sometimes" regretting reassignment surgery and 23 (46.0%) were not in a relationship. For the cohort, estradiol, testosterone, and sex hormone binding globulin levels were in the expected range for the reassigned gender. The SF-36 survey revealed that the subscale scores of the participants did not differ substantively from those of Dutch and U.S. women. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

The total FSFI score was 16.95 ± 10.04 out of a maximal 36. The FSFI scores averaged 2.8 (6 point maximum): satisfaction 1.16 ± 0.10 , desire 1.12 ± 0.10 , lubrication 1.37 ± 0.29 , orgasm 1.22 ± 0.29 , and pain 2.21 ± 2.46 . Though these numbers were reported in the study, data on test population controls were not provided.

A post hoc exploration of the data suggested the following: perceived improvement in general health status was greater in the subset that had undergone reassignment surgery within the last year; sexual orientation impacted the likelihood of being in a relationship; SF-36 scores for vitality, social functioning, and mental health were nominally better for those in relationships, but that overall SF-36 scores did not differ by relationship status; sexual orientation and being in a relationship impacted FSFI scores; and reported sexual function was higher in those with higher satisfaction with regards to their appearance.

Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. *Quality of life and sexual health after sex reassignment surgery in transsexual men. J Sex Med.* 2011 Dec;8 (12):3379-88. Epub 2011 Jun 23.

Wierckx et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments (a non-specific quality of life tool with reported normative data along with three self-designed tools). The investigators assessed general quality of life, sexual relationships, and surgical complications in Dutch-speaking female-to-male patients with gender dysphoria who attended a single-center, specialized, comprehensive care, university clinic (Ghent, Belgium). Investigators used the Dutch version of the SF-36 with 36 questions, eight subscales, and two domains evaluating physical and mental health. Results were compared to normative data from Dutch women and Dutch men. Self-designed questionnaires to evaluate aspects of medical history, sexual functioning (there were separate versions for those with and without partners), and surgical results were also used. The Likert-style format was used for many of the questions.

A total of 79 female-to-male patients with gender dysphoria had undergone reassignment surgery were recruited; ultimately, 47 (59.5%) chose to participate. Three additional patients were recruited by other patients. One of the 50 participants was later excluded for undergoing reassignment surgery within the one year window. The age of patients was: 30 ± 8.2 years (range 16 to 49) at the time of reassignment surgery and 37.1 ± 8.2 years (range 22 to 54) at the time of follow-up. The time since hysterectomy, oophorectomy, and mastectomy was 8 years (range 2 to 22). The patient population had undergone additional surgical procedures: metoidioplasty (n=9; 18.4%), phalloplasty (n=8 after metoidioplasty, 38 directly; 93.9% total), and implantation of erectile prosthetic device (n=32; 65.3%). All had started hormonal therapy at least two years prior to surgery and continued to use androgens.

The SF-36 survey was completed by 47 (95.9%) participants. The "Vitality" and the "Mental Health" scales were lower than the Dutch male population: 62.1 ± 20.7 versus 71.9 ± 18.3 and 72.6 ± 19.2 versus 79.3 ± 16.4 respectively. These subscale scores were equivalent to the mean scores of the Dutch women.

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None of the participants were dissatisfied with their hysterectomy-oophorectomy procedures; 4.1% were dissatisfied with their prostatectomies because of sexual side effects, and 1% were dissatisfied with their phalloplasties. Of the participants, 17.9% were dissatisfied with the implantation of an erectile prosthetic device; 25 (51.0%) reported at least one post-operative complication associated with phalloplasty (e.g., infection, urethrostenosis, or fistula formation); 16 (50.0% of the 32 with an erectile prosthetic device) reported at least one post-operative complication associated with implantation of an erectile prosthetic (e.g., infection, leakage, incorrect positioning, or lack of function).

A total of 18 (36.7%) participants were not in a relationship; 12.2% reported the inability to achieve orgasm with self-stimulation less than half the time; 12.2% did not respond to the question. Of those participants with partners, 28.5% reported the inability to achieve orgasm with intercourse less than half the time and 9.7% did not respond to this question. Also, 61.3% of those with partners reported (a) no sexual activities (19.4%) or (b) activities once or twice monthly (41.9%), and there were 12.9% who declined to answer.

c. Observational, surgical patients, cross-sectional, with controls

Ainsworth TA, Spiegel JH. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. Qual Life Res. 2010 Sep;19(7):1019-24.

Ainsworth and Spiegel conducted a prospective, observational study using a cross-sectional design and a partially self-designed survey tool. The blind status is unknown. Treatment types served as the basis for controls.

The investigators, head and neck surgeons who provided facial feminization services, assessed perception of appearance and quality of life in male-to-female subjects with self-reported gender dysphoria. Patients could have received no therapeutic intervention, hormone therapy, reassignment surgery, and/or facial feminization surgery and an unrestricted length of transition. (Transition refers to the time when a transgender person begins to live as the gender with which they identify rather than the gender assigned at birth.) Criteria for the various types of interventions were not available because of the survey design of the study. Patients were recruited via website or at a 2007 health conference. Pre-specified controls to eliminate duplicate responders were not provided. The investigators employed a self-designed Likert-style facial feminization outcomes evaluation questionnaire and a "San Francisco 36" health questionnaire. No citations were provided for the latter. It appears to be the Short-form (SF) 36-version 2. Changes or differences considered to be biologically significant were not pre-specified. Power corrections for multiple comparisons were not provided.

The investigators reported that there were 247 participants. (The numbers of incomplete questionnaires was not reported.) Of the 247 participants, 25 (10.1%) received only primary sex trait reassignment surgery, 28 (11.3%) received facial surgery without primary sex trait reassignment surgery, 47 (19.0%) received both facial and primary sex trait reassignment surgery, and 147 (59.5%) received neither facial nor reassignment surgery.

The mean age for each of these cohorts was 50 years (no standard deviation [S.D.]) only reassignment surgery, 51 years (no S.D.) only facial surgery, 49 years (no S.D.) both types of surgery, and 46 years (no S.D.) (neither surgery). Of the surgical cohorts: 100% of those who had undergone primary sex trait reassignment surgery alone used hormone therapy, 86% of those who had undergone facial feminization used hormone therapy, and 98% of those who had undergone both primary sex trait reassignment surgery and facial feminization used hormone therapy. In contrast to the surgical cohorts, 66% of the "no surgery" cohort used hormonal therapy, and a large proportion (27%) had been in transition for less than one year.

The investigators reported higher scores on the facial outcomes evaluation in those who had undergone facial feminization. Scores of the surgical cohorts for the presumptive SF-36 comprehensive mental health domain did not differ from the general U.S. female population. Scores of the "no surgery" cohort for the comprehensive mental health domain were statistically lower than those of the general U.S. female population, but within one standard deviation of the normative mean. Mean scores of all the gender dysphoric cohorts for the comprehensive physical domain were statistically higher than those of the general female U.S. population, but were well within one standard deviation of the normative mean. Analyses of inter-cohort differences for the SF-36 results were not conducted. Although the investigators commented on the potential disproportionate impact of hormone therapy on outcomes and differences in the time in "transition", they did not conduct any statistical analyses to correct for putative confounding variables.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology. 2008;41(2):96-100. Epub 2007 Nov 23.

Kraemer et al. conducted a single center (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design comparing pre-and post- surgical cohorts. Patients were required to meet DSM III or DSM IV criteria as applicable to the time of entry into the clinic. Post-surgical patients were from a long-term study group (Hepp et al., 2002). Pre-surgical patients were recent consecutive referrals. The assessment tool was the Fragebogen zur Beurteilung des eigenen Körpers (FBek) which contained three domains.

There were 23 pre-operative patients: 7 (30.4%) female-to-male and 16 (69.6%) male-to-female (ratio 1:2.3). There were 22 post-operative patients: 8 (36.4 %) female-to-male and 14 (63.6%) male-to-female (ratio 1:1.8). The mean ages of the cohorts were as follows: pre-operative 33.0 ± 11.3 years; post-operative 38.2 ± 9.0 years. The mean duration after reassignment surgery was 51 ± 25 months (range 5-96).

The pre-operative groups had statistically higher insecurity scores compared to normative data for the natal sex: female-to-male 9.0 ± 3.8 versus 5.1 ± 3.7 ; male-to-female 8.1 ± 4.5 versus 4.7 ± 3.1 as well as statistically lower self-confidence in one's attractiveness: female-to-male 3.1 ± 2.9 versus 8.9 ± 3.1 ; male-to-female 7.0 ± 2.9 vs 9.5 ± 2.6 .

Mate-Kole et al. conducted a single site (London, United Kingdom) prospective non-blinded, observational study using a cross-sectional design and two psychological tests (one with some normative data). Concurrent controls were used in this study design. The investigators assessed neuroticism and sex role in natal males with gender dysphoria. Patients at various stages of management, (i.e., under evaluation, using cross-sex hormones, or post reassignment surgery [6 months to 2 years]) were matched by age of cross-dressing onset, childhood neuroticism, personal psychiatric history, and family psychiatric history. Both a psychologist and psychiatrist conducted assessments. The instruments used were the Crown Crisp Experiential Index (CCEI) for psychoneurotic symptoms and the Bem Sex Role Inventory. ANOVA was used to identify differences between the three treatment cohorts.

For each cohort, investigators recruited 50 male-to-female patients from Charing Cross Hospital. The mean ages of the three cohorts were as follows: 34 years for patients undergoing evaluation; 35 years for wait-listed patients; and 37 years for post-operative patients. For the cohorts, 22% of those under evaluation, 24% of those on hormone treatment only, and 30% of those post-surgery had prior psychiatric histories, and 24%, 24%, while 14% in each cohort, respectively, had a history of attempted suicide. More than 30% of patients in each cohort had a first degree relative with a history of psychiatric disease.

The scores for the individual CCEI domains for depression and somatic anxiety were statistically higher (worse) for patients under evaluation than those on hormone treatment alone. The scores for all of the individual CCEI domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were statistically lower in the post-operative cohort than in the other two cohorts.

The Bem Sex Role Inventory masculinity score for the combined cohorts was lower than for North American norms for either men or women. The Bem Sex Role Inventory femininity score for the combined cohorts was higher than for North American norms for either men or women. Those who were undergoing evaluation had the most divergent scores from North American norms and from the other treatment cohorts. Absolute differences were small. All scores of gender dysphoric patients averaged between 3.95 and 5.33 on a 7 point scale while the normative scores averaged between 4.59 and 5.12.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. Arch Sex Behav. 2001 Jun;30(3):301-10.

Wolfradt and Neumann conducted a controlled, prospective, non-blinded, observational study using a cross-sectional design. The investigators assessed aspects of personality in male-to-female patients who had undergone vocal cord surgery for voice feminization and in healthy non-transgender volunteers from the region. The patients had undergone gender reassignment surgery 1 to 5 years prior to voice surgery. The volunteers were matched by age and occupation.

The primary hypothesis was that depersonalization, with the sense of being detached from one's body or mental processes, would be more common in male-to-female patients with gender dysphoria. German versions of the Scale for Depersonalization Experiences (SDPE), the Body Image Questionnaire (BIQ), a Gender Identity Trait Scale (GIS), and the Self-Esteem Scale (SES) were used in addition to a question regarding global satisfaction. Three of the assessments used a 5 point scale (BIQ, GIS, and SDPE) for questions. One used a 4 point scale (SES). Another used a 7 point scale (global satisfaction). The study consisted of 30 male-to-female patients, 30 healthy female volunteers, and 30 healthy male volunteers. The mean age of study participants was 43 years (range 29- 67).

Results of the study revealed that there were no differences between the three groups for the mean scores of measures assessing depersonalization, global satisfaction, the integration of masculine traits, and body-image-rejected (subset). Also, the sense of femininity was equivalent for male-to-female patients and female controls and higher than that in male controls. The levels of self-esteem and body image-dynamic (subset) were equivalent for male-to-female patients and male controls and higher than that in female controls, and none of the numeric differences between means exceeded 0.61 units.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril. 2009 Nov;92(5):1685-1689.e3. Epub 2008 Nov 6.

Kuhn et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and semi-matched control cohort. The investigators assessed global satisfaction in patients who were from gynecology and endocrinology clinic (Bern, Switzerland), and who had undergone some aspect of gender reassignment surgery in the distant past, but were still receiving cross-sex hormones from the clinic. The quality of life assessment tools included a VAS and the King's Health Questionnaire (KHQ), which consists of eight domains with scores between zero and five or one and five, with lower scores indicating higher preference. The KHQ and the numerical change/difference required for clinical significance (≥ 5 points in a given domain, with higher scores being more pathologic) were included in the publication. Twenty healthy female controls from the medical staff who had previously undergone an abdominal or pelvic surgery were partially matched by age and body mass index (BMI), but not sex. No corroborative gynecologic or urologic evaluations were undertaken.

Of the 55 participants, three (5.4%) were female-to-male and 52 (94.5%) were male-to-female (ratio 1:17.3). Reassignment surgery had been conducted 8 to 23 years earlier (median 15 years). The median age of the patients at the time of this study was 51 years (range 39-62 years). The patients had undergone a median of nine surgical procedures in comparison to the two undergone by controls. Reassignment patients were less likely to be married (23.6% versus 65%; $p=0.002$); partnership status was unknown in five patients. The scores of VAS global satisfaction (maximal score eight) were lower for surgically reassigned patients (4.49 ± 0.1 SEM) than controls (7.35 ± 0.26 SEM) ($p<0.0001$).

The abstract stated that quality of life was lower in reassignment patients 15 years after surgery relative to controls. One table in the study, Table 2, delineated statistically and biologically significant differences for four of the eight KHQ domains between the patients and controls: physical limitation: 37.6 ± 2.3 versus 20.9 ± 1.9 ($p<0.0001$), personal limitation: 20.9 ± 1.9 versus 11.6 ± 0.4 ($p<0.001$), role limitation: 27.8 ± 2.4 versus 34.6 ± 1.7 ($p=0.046$), and general health: 31.7 ± 2.2 versus 41.0 ± 2.3 ($p<0.02$). There is a related paper by Kuhn

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand. 2000 Oct;102(4):276-81.

Haraldsen and Dahl conducted a single-center (Oslo, Norway) partially prospective, non-blinded, observational study using a cross-sectional design and a non-specific psychometric test. There was a control group, but it was not concurrent.

In the germane sub-study, the investigator assessed psychopathology in patients with gender dysphoria. Patients, who were independently evaluated by two senior psychiatrists, were required to meet DSM III-R or DSM IV diagnostic criteria and the Swedish criteria for reassignment surgery. The Norwegian version of the SCL-90 was used. The testing was conducted from 1987 to 1989 for those who had undergone reassignment surgery between 1963 and 1987 and from 1996 to 1998 for pre- surgical patients who had applied for reassignment surgery between 1996 and 1998. In addition, Axis I, Axis II, and Axis V (Global Functioning) was assessed.

Of 65 post-surgical and 34 pre-surgical patients, 59 post-surgical and 27 pre-surgical patients ultimately entered the study. The combined cohorts consisted of 35 (40.7%) female-to-male patients and 51 (59.3%) male-to-female patients (ratio 1:1.5). The ages were female-to-male 34 ± 9.5 years and female-to-male 33.3 ± 10.0 years. The other control group consisted of patients with personality disorder. Of these, 101 (27 men (33.9 ± 7.3 years) and 74 women (31.6 ± 8.2)) were tested during a treatment program. One year later, 98% were evaluated. A total of 28 (32.5%) of the pre- and post- reassignment surgery patients had an Axis I diagnosis compared to 100 (99.0%) of those with personality disorders. Depression and anxiety were the most common diagnoses in both groups, but were approximately three to four times more common in the personality disorder cohort. Seventeen (19.8%) of the pre- and post-reassignment surgery patients had an Axis II diagnosis whereas the mean number of personality disorders in the personality disorder cohort was 1.7 ± 1 . The Global Assessment of Function was higher (better) in the gender dysphoric groups (78.0 ± 8.9) than in the personality disorder cohort (53.0 ± 9.0).

Global Severity Indices (GSI) were highest for those with personality disorder regardless of gender and exceeded the cut-point score of 1.0. The GSI scores for females-to-males and males-to-females were 0.67 ± 0.57 and 0.56 ± 0.45 . Although they were nominally higher than the healthy normative controls (males: 0.32 ± 0.36 and females 0.41 ± 0.43), they were well within the non- pathologic range. The same was true for the subscales.

SCL-90 GSI scores did not differ substantively between pre- and post-surgical patients, nor did the SCI subscale scores differ substantively between pre- and post-surgical patients. Any small non-significant differences tracked with the age and sex differences.

Beatrice conducted a prospective, non-blinded, observational study using a cross-sectional design and control cohorts in the U.S. The investigator assessed psychological adjustment and functioning (self-acceptance) in male-to-female patients with gender dysphoria (with and without GRS), transvestites from two university specialty clinics, and self-identified heterosexual males recruited from the same two universities. The criteria to qualify for the study included being known to the clinic for at least one year, cross-dressing for at least one year without arrest, attendance at 10 or more therapy sessions, emotionally self-supporting, and financially capable of payment for reassignment surgery, and all of these criteria were met by the pre-operative cohort as well as the post-operative cohort. The cohorts were matched to the post-operative cohort (age, educational level, income, ethnicity, and prior heterosexual object choice). The post-operative cohort was selected not on the basis of population representation, but on the basis of demographic feasibility for a small study. The instruments used were the Minnesota Multiphasic Personality Inventory (MMPI) and the Tennessee Self-Concept Scale (TSCS). Changes or differences considered to be biologically significant were not pre-specified.

Of the initial 54 recruits, ten subjects were left in each of the cohorts because of exclusions identified due to demographic factors. The mean age of each cohort were as follows: pre-operative gender dysphoric patients 32.5 (range 27-42) years, postoperative patients 35.1 (30-43) years old, transvestite 32.5 (29-37) years old, and heterosexual male 32.9 (28-38) years old. All were Caucasian. The mean age for cross-dressing in pre-operative patients (6.4 years) and post-operative patients (5.8 years) was significantly lower than for transvestites (11.8 years).

The scores for self-acceptance did not differ by diagnostic category or surgical status as measured by the TSCS instrument. As measured by the T-scored MMPI instrument (50 ± 10), levels of paranoia and schizophrenia were higher for post-operative (GRS) patients (63.0 and 68.8) than transvestites (55.6 and 59.6) and heterosexual males (56.2 and 51.6). Levels of schizophrenia were higher for pre-operative patients (65.1) than heterosexual males (51.6). There were no differences between patients with gender dysphoria. Scores for the Masculine-Feminine domain were equivalent in those with transvestitism and gender dysphoria with or without surgery, but higher than in heterosexual males. The analysis revealed that despite the high level of socio-economic functioning in these highly selected subjects, the MMPI profiles based on the categories with the highest scores were notable for antisocial personality, emotionally unstable personality, and possible manic psychosis in the pre-operative GRS patients and for paranoid personality, paranoid schizophrenia, and schizoid personality in the post-operative GRS patients. By contrast, the same MMPI profiling in heterosexual males and transvestites was notable for the absence of psychological dysfunction.

d. Observational, surgical patients, longitudinal, with controls

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One*. 2011;6(2):e16885. Epub 2011 Feb 22.

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Dhejne et al. conducted a retrospective, non-blinded, observational study of nation-wide mortality using a longitudinal case-control design. The investigators assessed conditions ages 12-23, not limited to, mortality, suicide attempts, psychiatric hospitalization, and substance abuse in gender-reassigned persons and randomly selected unexposed controls matched by birth year and natal sex (1:10) as well as by birth year and the reassigned gender (1:10). Data were extracted from national databases including the Total Population Register (Statistics Sweden), the Medical Birth Register, the Cause of Death Register (Statistics Sweden), the Hospital Discharge Register (National Board of Health and Welfare), the Crime Register (National Council of Crime), and those from the Register of Education for highest educational level. The criteria required to obtain the initial certificate for reassignment surgery and change in legal status from the National Board of Health and Welfare were the 2002 WPATH criteria and included evaluation and treatment by one of six specialized teams, name change, a new national identity number indicative of gender, continued use of hormones, and sterilization/castration. Descriptive statistics with hazard ratios were provided.

Investigators identified 804 patients with gender identity disorder (or some other disorder) in Sweden during the period from 1973 to 2003 inclusive. Of these patients, 324 (40.3%) underwent gender-reassignment surgery (133 female-to-male [41.0%]; 191 male-to-female [59.0%]; ratio 1:1.4). The average follow-up time for all-cause mortality was 11.4 years (median 9.1). The average follow-up time for psychiatric hospitalization was 10.4 years (median 8.1).

The mean ages in female-to-male and male-to-female reassigned patients were: 33.3 ± 8.7 (range 20–62) and 36.3 ± 10.1 (range 21–69) years, respectively. Immigrant status was two times higher in reassigned patients ($n=70$, 21.6%) than in either type of control (birth [natal] sex matched $n=294$ [9.1%] or reassigned gender matched $n=264$ [8.1%]). Educational attainment (10 or more years) was somewhat lower for reassigned patients ($n=151$ [57.8%]) than in either type of control (birth sex matched $n=1,725$ [61.5%] or reassigned gender matched $n=1804$ [64.3%]) (cohort data were incomplete). The biggest discordance in educational attainment was for female-to-male reassigned patients regardless of the control used. Prior psychiatric morbidity (which did not include hospitalization for gender dysphoria) was more than four times higher in reassigned patients ($n=58$, 17.9%) than in either type of control (birth sex matched $n=123$ [3.8%] or reassigned gender matched $n=114$ [3.5%]).

All-cause mortality was higher for patients who underwent gender reassignment surgery ($n=27$ [8.3%]) than in controls (hazard ratio 2.8 [CI 1.8-4.3]) even after adjustment for covariants (prior psychiatric morbidity and immigration status). Divergence in the survival curves began at 10 years. Survival rates at 20 year follow-up (as derived from figure 1) were: female control 97%, male controls 94%, female-to-male patients 88%, and male-to-female patients 82%. The major contributor to this mortality difference was completed suicide ($n=10$ [3.1%]; adjusted hazard ratio 19.1 [CI 5.8-62.9]). Mortality due to cardiovascular disease was modestly higher for reassigned patients ($n=9$ [2.8%]) than in controls (hazard ratio 2.5 [CI 1.2-5.3]).

Suicide attempts were more common in patients who underwent gender reassignment surgery ($n=29$ [9.0%]) than in controls (adjusted hazard ratio 4.9 [CI 2.9–8.5]). Male-to-female patients were at higher adjusted risk for attempted suicide than either control whereas female-to-male patients were at higher adjusted risk compared to only male controls and maintained the female pattern of higher attempted suicide risk. Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common in reassigned persons $n=64$ [20.0%] than in controls (hazard ratio 2.8 [CI 2.0–3.9]) even after adjusting for prior psychiatric morbidity. Hospitalization for substance abuse was not greater than either type of control.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. Arch Sex Behav. 2014 Nov;43(8):1535-45. Epub 2014 May 29 and Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand. 1998 Apr;97(4):284 (Dhejne et al., 2014; Landén et al., 1998) Sweden-All

Dhejne et al. conducted a non-blinded, observational study that was longitudinal for the capture of patients with "regret" in a national database. This same group (Landén et al., 1998) conducted a similar study along with retrospective acquisition of clinical data to explore the differences between the cohorts with and without regret. There were no external controls; only intra- group comparisons for this surgical series.

The investigators assessed the frequency of regret for gender reassignment surgery. Data were extracted from registries at the National Board of Health and Welfare to which patients seeking reassignment surgery or reversal of reassignment surgery make a formal application and which has maintained such records since a 1972 law regulating surgical and legal sex reassignment. The investigators reviewed application files from 1960 through 2010. The specific criteria to qualify for gender surgery were not delineated. Patients typically underwent diagnostic evaluation for at least one year. Diagnostic evaluation was typically followed by the initiation of gender confirmation treatment including hormonal therapy and real-life experience. After two years of evaluation and treatment, patients could make applications to the national board. Until recently sterilization or castration were the required minimal surgical procedures (Dhejne et al., 2011). Secular changes in this program included consolidation of care to limited sites, changes in accepted diagnostic criteria, and provision of non-genital surgery, e.g., mastectomy during the real- life experience phase, and family support.

There were 767 applicants for legal and surgical reassignment (289 [37.7%] female-to-male and 478 [62.3%] male-to-female; ratio 1:1.6). The number of applicants doubled each ten year interval starting in 1981.

Of the applicants, 88.8% or 681 (252 [37.0%] female-to-male and 429 [63.0%] male-to-female; ratio 1:1.7] had undergone surgery and changed legal status by June 30, 2011. This number included eight (four [50.0%] female-to-male and four [50.0%] male to female; ratio 1:1) people who underwent surgery prior to the 1972 law. This number appears to include 41 (two [4.9%] female-to-male and 39 [95.1%] male-to-female; ratio 1:19.5) people who underwent surgery abroad at their own expense (usually in Thailand or the U.S.). This cohort (6% of 681) includes one person who was denied reassignment surgery by Sweden.

Twenty-five (3.3%) of the applications were denied with the two most common reasons being an incomplete application or not meeting the diagnostic criteria. An additional 61(8.0%) withdrew their application, were wait-listed for surgery, postponed surgery (perhaps in hopes of the later revocation of the sterilization requirement), or were granted partial treatment.

The formal application for reversal of the legal gender status, the "regret rate", was 2.2%. No one who underwent sex- reassignment surgery outside of Sweden (36 of these 41 had surgery after 1991) has requested reversal. The authors noted, however, that this preliminary number may be low because the median time interval to reversal request was eight years-only three of which had elapsed by publication submission- and because it was the largest serial cohort. This number did not include other possible expressions of regret including suicide (Dhejne et al., 2011).

Dhejne et al. in 2014 reported that the female-to-male (n=5): male-to-female (n=10) ratio among those who made formal applications for reversal was 1:2. The investigators also reported that the female-to-male applicants for reversal were younger at the time of initial surgical application (median age 22 years) than the complete female-to-male cohort at the time of surgical application (median age 27 years). By contrast the male-to-female applicants for reversal were older at the time of initial surgical application (median age 35 years) than the complete male-to-female cohort at the time of initial surgical application (median age 32 years). Other clinical data to explore the differences between the cohorts with and without regret were not presented in this update publication.

In their earlier publication, in addition to determining a regret rate (3.8%), Landén et al. extracted data from medical records and government verdicts. Pearson Chi-square testing with Yates' correction for small sample sizes was used to identify candidate variables predictive of regret. They observed that: (a) 25.0% of the cohort with regrets and 11.4% of the cohort without regrets were unemployed, (b) 16.7% of the cohort with regrets and 15.4% of the cohort without regrets were on "sick benefit", (c) 15.4% of the cohort with regrets and 13.9% of the cohort without regrets had problems with substance abuse, (d) 69.2% of the cohort with regrets and 34.6% of the cohort without regrets had undergone psychiatric treatment, (e) 15.4% of the cohort with regrets and 8.8% of the cohort without regrets had a mood disorder, and (f) 15.4% of the cohort with regrets and 1.5% of the cohort without regrets had a psychotic disorder.

The putative prognostic factors that were statistically different between the cohorts with and without regret included prior psychiatric treatment, a history of psychotic disorder, atypical features of gender identity, and poor family support. Factors that trended towards statistical difference included having an unstable personality, sexual orientation and transvestitism. Univariate regression analyses further clarified the most important variables. These variables were tested with logistic regression. Initial modeling included the variable "history of psychotic disorder". Although this variable was predictive, it was excluded from future analyses because it was already a contraindication to reassignment surgery. Additional multivariate regression analyses identified poor family support as the most predictive variable and atypical features of gender identity as the second most important variable. Presence of both variables had a more than additive effect.

The nationwide mortality studies by Dhejne et al. (2011) includes much, if not all, of the Landén (1998) patient population and most of the Dhejne (2014) population. There is a related paper by Landén et al. 1998b that included the criteria to qualify for surgical intervention at that time.

Heylens et al. conducted a prospective, non-blinded observational study using a longitudinal design in which patients served as their own controls. They used a non-specific psychiatric test with normative data along with two self-designed questionnaires. The investigators assessed psychosocial adjustment and psychopathology in patients with gender identity disorders. Patients were to be sequentially evaluated prior to institution of hormonal therapy, then 3 to 6 months after the start of cross-sex hormone treatment, and then again one to 12 months after reassignment surgery. The Dutch version of the SCL-90R with eight subscales (agoraphobia, anxiety, depression, hostility, interpersonal sensitivity, paranoid ideation/psychoticism, and sleeping problems) and a global score (psycho-neuroticism) was used serially. A seven parameter questionnaire was used serially to assess changes in social function. Another cross-sectional survey assessed emotional state. The cohorts at each time point consisted of patients who were in the treatment cohort at the time and who had submitted survey responses.

Ninety of the patients who applied for reassignment surgery between June 2005 and March 2009 were recruited. Fifty seven entered the study. Forty-six (51.1% of the recruited population) underwent reassignment surgery. Baseline questionnaire information was missing for 3 patients. Baseline SCL-90 scores were missing for 1 patient but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. Time point 2 (after hormone therapy) SCL-90 information was missing for 10, but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. At time point 3, 42 (91.3% of those who underwent reassignment surgery) patients completed some part of the SCL-90 survey and the psychosocial questionnaires. Some questionnaires were incomplete. The investigators reported response rates of 73.7% for the psychosocial questionnaires and 82.5% for the SCL-90.

Of those who responded at follow-up after surgery, 88.1% reported having good friends; 52.4% reported the absence of a relationship; 47.6% had no sexual contacts; 42.9% lived alone; 40.5% were unemployed, retired, students, or otherwise not working; 2.4% reported alcohol abuse; and 9.3% had attempted suicide. The frequency of these parameters reportedly did not change statistically during the study interval, but there was no adjustment for the inclusion of patients who did not undergo surgery.

In a cross-sectional, self-report mood survey, of the 42 study entrants who completed the entire treatment regimen including reassignment surgery and the final assessment (refers to the initial 57) reported improved body-related experience (97.6%), happiness (92.9%), mood (95.2%), and self-confidence (78.6%) and reduced anxiety (81.0%). Of participants, 16.7% reported thoughts of suicide. Patients also reported on the intervention phase that they believed was most helpful: hormone initiation (57.9%), reassignment surgery (31.6%), and diagnostic-psychotherapy phase (10.5%).

The global "psycho-neuroticism" SCL-90R score, along with scores of 7 of the 8 subscales, at baseline were statistically more pathologic than the general population. After hormone therapy, the score for global "psycho-neuroticism" normalized and remained normal after reassignment surgery. More specifically the range for the global score is 90 to 450 with higher scores being more pathologic. The score for the general population was 118.3 ± 32.4 . The respective scores for the various gender dysphoric cohorts were 157.7 ± 49.8 at initial presentation, 119.7 ± 32.1 after hormone therapy, and 127.9 ± 37.2 after surgery. The scores for the general population and the scores after either hormone treatment or surgical treatment did not differ.

Kockott and Fahrner conducted a single center (Munich, Germany) prospective, observational study using a longitudinal design. Treatment cohorts were used as controls, and patients served as their own controls. The investigators assessed psychosocial adjustment in patients with gender identity issues. Patients were to have met DSM III criteria. Trans-sexuality, transvestitism, and homosexuality were differentiated. The criteria required for patients to receive hormone therapy and/or reassignment surgery were not delineated. After receiving hormone therapy, patients were later classified by surgical reassignment status (pre-operative and post-operative) and desire for surgery (unchanged desire, hesitant, and no longer desired).

The first investigative tool was a semi-structured in-person interview consisting of 125 questions. The second investigative tool was a scale that organized the clinical material into nine domains which were then scored on a scale. The Psychological Integration of Trans-sexuals (PIT) instrument developed according to the scale used by Hunt and Hampson (1980) for assessment of 17 post-operative patients. There were 15 interviews and two separate interviewers. There were 80 patients identified, but 58 (72.5%) patients (26 pre-operative; 32 post-operative) were ultimately included in the analysis. The duration of follow-up was longer for post-operative patients (6.5 years) than for pre-operative patients (4.6 years) (including time for one patient subsequently excluded). The mean age of the post-operative patients was 35.5 ± 13.1 years, and the age of the patients who maintained a continued desire for surgery was 31.7 ± 10.2 years. The age of the patients who hesitated about surgery was somewhat older, 40.3 ± 9.4 years. The age of the patients who were no longer interested in surgery was 31.8 ± 6.5 years. All were employed or in school at baseline. Patients with hesitation were financially better-off, had longer-standing relationships even if unhappy, and had a statistical tendency to place less value on sex than those with an unchanged wish for surgery.

Post-operative patients more frequently reported contentment with the desired gender and the success of adaption to the gender role than the pre-operative patients with a persistent desire for surgery. Post-operative patients more frequently reported sexual satisfaction than pre-operative patients with a continuing desire for surgery. Post-operative patients also more frequently reported financial sufficiency and employment than pre-operative patients with a persistent desire for surgery. Suicide attempts were stated to be statistically less frequent in the post-surgical cohort.

Psychosocial adjustment scores were in the low end of the range with "distinct difficulties" (19-27) at the initial evaluation for the post-operative patients (19.7), the pre-operative patients with a persistent wish for surgery (20.2), and the hesitant patients (19.7). At initial evaluation, psychosocial adjustment scores for patients no longer wanting surgery were at the high end of the range with "few difficulties" (10-18). At the final evaluation, Psychosocial adjustment scores were at the high end of the range "few difficulties" (10-18) for the post-operative patients (13.2) and the patients no longer wanting surgery (16.5). Psychosocial adjustment scores at the final evaluation were in the borderline range between "few difficulties" (10-18) and "distinct difficulties" (19-27) for both the pre-operative patients with a persistent desire for surgery (18.7), and the hesitant patients (19.1).

The changes in the initial score and the final follow-up score within each group were tracked and reported to be statistically significant for the post-operative group, but not for the other groups. Statistical differences between groups were not presented. Moreover, the post-operative patients had an additional test immediately prior to surgery. The first baseline score (19.7) would have characterized the patients as having "distinct difficulties" in
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psychosocial adjustment while the second baseline score (16.7) would have categorized the patients as having "few difficulties in psychosocial adjustment despite the absence of any intervention except age of onset of having imminent reassignment surgery. No statistics reporting on the change between scores of the initial test and the test immediately prior to surgery and the change between scores of the test immediately prior to surgery and the final follow-up were provided.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry. 1979 Aug;36(9):1010-5. (United States study)

Meyer and Reter conducted a single-center (Baltimore, Maryland, U.S.) prospective, non-blinded, observational study using a longitudinal design and retrospective baseline data. Interview data were scored with a self-designed tool. There were treatment control cohorts, and patients served as their own controls. The investigators assessed patients with gender dysphoria. The 1971 criteria for surgery required documented cross-sex hormone use as well as living and working in the desired gender for at least one year in patients subsequently applying for surgery. Clinical data including initial interviews were used for baseline data. In follow-up, the investigators used extensive two to four hour interviews to collect information on (a) objective criteria of adaptation, (b) familial relationships and coping with life milestones, and (c) sexual activities and fantasies. The objective criteria, which were the subject of the publication, included employment status (Hollingshead job level), cohabitation patterns, and need for psychiatric intervention. The investigators designed a scoring mechanism for these criteria and used it to determine a global adjustment score. The score value or the change score that was considered to be biologically significant was not pre-specified in the methods.

The clinic opened with 100 patients, but when the follow-up was completed, 52 patients were interviewed and 50 gave consent for publication. Of these, 15 (four female-to-male, 11 male-to-female; ratio 1:2.8) were part of the initial operative cohort, 14 (one female-to-male; 13 male-to-female; ratio 1:13) later underwent reassignment surgery at the institution or elsewhere, and 21 (five female-to-male; 16 male-to-female; ratio 1:3.2) did not undergo surgery. The mean ages of these cohorts were 30.1, 30.9, and 26.7 years respectively. The mean follow-up time was 62 months (range 19-142) for those who underwent surgery and 25 months (range 15-48) for those who did not. Socioeconomic status was lowest in those who subsequently underwent reassignment surgery.

Of patients initially receiving surgery, 33% had some type of psychiatric contact prior to the initial clinic evaluation and 8% had psychiatric contact during the follow-up. Of the patients who had not undergone surgery or who had done so later, 72% had some type of psychiatric contact prior to the initial clinic evaluation and 28% had psychiatric contact during follow-up. There was a single female-to-male patient with multiple surgical complications who sought partial reassignment surgery reversal.

The adjustment scores improved over time with borderline statistical significance for the initial operative group and with statistical significance for the never operated group. The absolute score value at follow-up was the same for both groups (1.07+1.53 and 1.10+1.97 respectively). By contrast, the adjustment scores did not improve for those who were not in the cohort initially approved for surgery, but who subsequently underwent surgery later. This was particularly true if the surgery was performed elsewhere. The absolute score value at follow-up was 0.21+1.89.

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. Arch Sex Behav. 1996 Oct;25(5):515-25.

Rakic et al. single-center (Belgrade, Yugoslavia) conducted a prospective, non-blinded, observational study using a cross-sectional design and an investigator- designed quality of life tool that asked longitudinal (pre- and post-treatment) questions. Patients served as their own controls. The authors state that the study was not designed to assess the predictors of poor outcomes.

The investigators assessed global satisfaction, body image, relationships, employment status, and sexual function in patients with gender dysphoria who underwent reassignment surgery between 1989 and 1993 and were at least six months post-operative. The criteria to qualify for gender surgery were delineated (1985 standards from the Harry Benjamin International Gender Dysphoria Association) and included cross-gender behavior for at least one year and sexual orientation to non-natal sex. The questionnaire consisted of 10 questions using yes/no answers or Likert-type scales. Findings were descriptive without statistical analysis. As such, changes or differences considered to be biologically significant were not pre-specified, and there were no adjustments for multiple comparisons.

Of the 38 patients who had undergone reassignment surgery, 34 were eligible for the study and 32 participated in the study (two were lost to follow-up and four were in the peri-operative period) - 10 (31.2%) female-to-male and 22 (68.8%) male-to-female (ratio 1:2.2). The duration of follow-up was 21.8 ± 13.4 months (range 6 months to 4 years). The age was female-to-male 27.8 ± 5.2 (range 23-37) and male-to-female 26.4 ± 7.8 (range 19-47).

Using an investigator-designed quality of life tool, all patients reported satisfaction with having undergone the surgery. Of the total participants, four (12.5%) (all male-to-female) and eight (25%) (87.5% male-to-female) reported complete dissatisfaction or partial satisfaction with their appearance. Regarding relationships, 80% of female-to-male and 100% of male-to-female patients were dissatisfied with their relationships with others prior to surgery; whereas, no female-to-male patients and 18.1% of male-to-female patients were dissatisfied with relationships after surgery. Regarding sexual partners, 60% of female-to-male and 72.7% of male-to-female patients reported not having a sexual partner prior to surgery; whereas, 20% of female-to-male patients and 27.3% of male-to-female patients did not have a sexual partner after surgery. Of those with partners at each time interval, 100% of female-to-male and 50% of male-to-female patients reported not experiencing orgasm prior to surgery; whereas, 75% of female-to-male and 37.5% of male-to-female patients reported not experiencing orgasm after surgery.

Rupp and Pfafflin conducted a single-center (Ulm, Germany) partially prospective, non-blinded, observational study using a longitudinal design and non-specific psychometric tests and a self-designed interview tool and questionnaire. Patients served as their own controls.

The investigators assessed psychological symptoms, interpersonal difficulties, gender role stereotypes, personality characteristics, societal function, sexual function, and satisfaction with new gender role in patients with gender dysphoria. Patients were required to have met the ICD-10 criteria for trans-sexualism, been seen by the clinic by prior to 2001, and completed an official change in gender including name change prior to 2001. Assessment tools included German versions of standardized surveys with normative data: the SCL 90R, the Inventory of Interpersonal Problems (IIP), Bem Sex Role Inventory (BSRI), and the Freiburg Personality Inventory (FPI-R), along with semi-structured interviews with self-designed questionnaires. The prospective survey results were compared to retrospective survey results. Changes or inter-group differences considered to be biologically significant were not pre-specified. Diagnostic cut points were not provided. Statistical corrections for multiple comparisons were not included.

Overall, 140 patients received recruitment letters and then 71 (50.7%) agreed to participate. Of these participants, 36 (50.7%) were female-to-male; 35 (49.3%) were male-to-female (ratio 1:0.97). The ages of the patients were: 41.2 ± 5.78 years (female-to-male) and 52.9 ± 10.82 years (male-to-female). The intervals for follow-up were 14.1 ± 1.97 years and 13.7 ± 2.17 years, respectively.

All female-to-male patients had undergone mastectomy; 91.7% had undergone oophorectomy and/or hysterectomy; 61.1% had undergone radial forearm flap phalloplasty or metaoidioplasty. Of male-to-female patients, 94.3% had undergone vaginoplasty and perhaps an additional procedure (breast augmentation, larynx surgery, or vocal cord surgery). Two male-to-female patients had not undergone any reassignment surgery, but were still included in the analyses.

A total of 68 patients ranked their well-being as 4.35 ± 0.86 out of five (three patients did not respond to this question). Of respondents, 40% reported not being in a steady relationship. Regular sexual relationships were reported by 57.1% of 35 female-to-male respondents and 39.4% of 33 male-to-female respondents (three patients did not respond to this question). A total of 11 patients reported receiving out-patient psychotherapy; 69 did not express a desire for gender role reversal (two did not respond to this question). The response rate was less than 100% for most of the self-designed survey questions.

Changes from the initial visit to the follow-up visit were assessed for the SCL-90R in 62 of 71 patients. The effect size was statistically significant and large only for the "Interpersonal Sensitivity" scale (one of 10 parameters). The absolute magnitude of mean change was small: from 0.70 ± 0.67 to 0.26 ± 0.34 (scale range 0-4). The duration of follow-up did not correlate with the magnitude of change on the various scales. Differences in baseline SCL-90R scores of 62 participants were compared with the score of 63 of the 69 eligible recruits who declined to enter the study and were notable for higher "Depression" scores for the latter.

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Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 55 of 71 patients. The effect size was statistically significant and large only for the "Overly Accommodating" scale (one of eight parameters). The absolute magnitude of mean change was small: from 11.64 ± 5.99 to 7.04 ± 4.73 (scale range 0-32). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 58 of 71 patients. The effect size was statistically significant and large only for the "Life Satisfaction" scale (one of 12 parameters). The absolute magnitude of mean change was substantive: from 4.43 ± 2.99 to 8.31 ± 2.63 (scale range 0-12). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the BSRI in 16 of 36 female to male patients and 19 of 35 male to female patients. The "Social Desirability" score increased for the female-to-male respondents. At endpoint, both categories of respondents reported androgynous self-images.

This current report is an update of prior publications by Pfafflin including work with Junge which was published in a variety of formats and initially in German.

Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med. 2005 Jan;35(1):89-99.

Smith et al. conducted a single-center (Amsterdam, Netherlands) prospective, non-blinded, observational study using a longitudinal design and psychological function tools. Patients served as their own control prior to and after reassignment surgery. The investigators assessed gender dysphoria, body dissatisfaction, physical appearance, psychopathology, personality traits, and post-operative function in patients with gender dysphoria. Patients underwent some aspect of reassignment surgery. The test instruments included the Utrecht Gender Dysphoria Scale (12 items), the Body Image Scale adapted for a Dutch population (30 items), Appraisal of Appearance Inventory (3 observers, 14 items), the Dutch Short MMPI (83 items), the Dutch version of the Symptom Checklist (SCL)(90 items), and clinic-developed or modified questionnaires. Pre-treatment data was obtained shortly after the initial interview. Post- surgery data were acquired at least one year post reassignment surgery.

Three hundred twenty five consecutive adolescents and adults were screened for the study. One-hundred three (29 [28.2%] female-to-male patients and 74 [71.8%] male-to-female patients [ratio 1:2.6]) never started hormone therapy; 222 (76 [34.2%] female-to-male patients and 146 [65.8%] male-to-female patients [ratio 1:1.9]) initiated hormone therapy. Of the patients who started hormone therapy, 34 (5 [14.7%] female-to-male patients and 29 [85.3%] male-to-female patients [ratio 1:5.8]) discontinued hormone therapy.

Subsequently, the study analysis was limited to adults. One hundred sixty-two (58 [35.8%] female-to-male and 104 [64.2%] male-to-female) patients were eligible and provided post-surgical test data, and 124 (77.8% of eligible adults) (49 [38.9%] female-to-male and 77 [61.1%] male-to-female [ratio 1:1.6]) provided post-surgical data. For those patients who completed reassignment, the mean age at the time of surgical request was 30.9 years (range 17.7-68.1) and 35.2 years (range 21.3-71.9) years at the time of follow-up. The intervals between hormone treatment initiation and surgery and surgery and follow-up were 20.4 months (range 12 to 73) and 21.3 months (range 12 to 47) respectively.

Of the 126 adults who provided post-surgical data, 50 (40.0%) reported having a steady sexual partner, three (2.3%) were retired, and 58 (46.0%) were unemployed. Regarding regret, six patients expressed some regret regarding surgery, but did not want to resume their natal gender role, and one male-to-female had significant regret and would not make the same decision.

Post-surgery Utrecht dysphoria scores dropped substantially and approached reportedly normal values. The patients' appearance better matched their new gender. No one was dissatisfied with his/her overall appearance at follow-up. Satisfaction with primary sexual, secondary sexual, and non-sexual body traits improved over time. Male-to-female patients, however, were more dissatisfied with the appearance of primary sex traits than female-to-male patients. Regarding mastectomy, 27 of 38 (71.1%) female-to-male respondents (not including 11 non-respondents) reported incomplete satisfaction with their mastectomy procedure. For five of these patients, the incomplete satisfaction was because of scarring. Regarding vaginoplasty, 20 of 67 (29.8%) male-to-female respondents (not including 10 non-respondents) reported incomplete satisfaction with their vaginoplasty.

Most of the MMPI scales were already in the normal range at the time of initial testing and remained in the normal range after surgery. SCL global scores for psycho- neuroticism were minimally elevated before surgery 143.0 ± 40.7 (scoring range 90 to 450) and normalized after surgery 120.3 ± 31.4 . (An analysis using patient level data for only the completers was not conducted.)

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to- female people before and after surgery. Sexual and Relationship Therapy. 2008 May; 23(2):141-5. (Not in PubMed) and Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. Sexual and Relationship Therapy. 2007 Feb; 22(1):77-81. (Not in PubMed)

Udeze et al. conducted a single-center (Leicester, United Kingdom) prospective, non-blinded, longitudinal study assessing a randomized subset of patients who had completed a non-specific psychological function tool prior to and after male-to-female reassignment surgery. Patients served as their own controls. The investigators used the WPATH criteria for patient selection. Psychiatric evaluations were routine. All patients selected for treatment were routinely asked to complete the self-administered SCL-90R voluntarily on admission to the program and post-operatively. A post-operative evaluations (psychiatric and SCL-90R assessment) were conducted within six months to minimize previously determined loss rates. The patient pool was domestic and international. There were 546 gender dysphoric patients from all over the United Kingdom and abroad, of whom 318 (58.2%) progressed to surgery. Of these, 127 were from the local Leicester area in the United Kingdom and 38 (29.9%) progressed to surgery. The mean age for the selected male-to-female patients at the time of study was 47.33 ± 13.26 years (range 25 to 80) and reflected an average wait time for surgery of 14 months (range 2 months to 6 years). For this investigation, 40 male-to-female subjects were prospectively selected.

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The raw SCL-90 global scores for psycho-neuroticism were unchanged over time: 48.33 prior to surgery and 49.15 after surgery. If the scale was consistent with T-scoring, the results were non-pathologic. No psychiatric disorders were otherwise identified prior to or after surgery.

Investigators from the same clinical group (Megeri, Khoosal, 2007) conducted additional testing to specifically address anxiety and depression with the Beck Depression Inventory, General Health Questionnaire (with 4 subscales), HADS, and Spielberger State and Trait Anxiety Questionnaire (STAI-X1 and STA-X2). The test population and study design appear to be the same. No absolute data were presented. Only changes in scores were presented. There were no statistically significant changes.

e. Randomized, surgical patients, longitudinal, with controls

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry. 1990 Aug;157:261-4.

Mate-Kole et al. conducted a prospective, non-blinded, controlled, randomized, longitudinal study using investigator-designed patient self-report questionnaires and non-specific psychological tests with some normative data. The investigators assessed neuroticism and sex role in natal males with gender dysphoria who had qualified for male-to-female reassignment surgery at a single-center specialty clinic (London, United Kingdom). Forty sequential patients were alternately assigned to early reassignment surgery or to standard wait times for reassignment surgery. Patients were evaluated after acceptance and 2 years later. The criteria used to qualify for gender surgery were the 1985 standards from the Harry Benjamin International Gender Dysphoria Association. These included a ≥ 2 year desire to change gender, a ≥ 1 year demonstrable ability to live and be self-supporting in the chosen gender, and psychiatric assessment for diagnosis and reassessment at six months for diagnostic confirmation and exclusion of psychosis.

Reassignment surgery was defined as orchidectomy, penectomy, and construction of a neo-vagina. The instruments used were the CCEI for psychoneurotic symptoms and the Bem Sex Role Inventory along with an incompletely described investigator-designed survey with questions about social life and sexual activity.

The mean age and range of the entire cohort was 32.5 years (21-53). Members of the early surgery cohort had a history of attempted suicide (one patient), psychiatric treatment for non-gender issues (six patients), and first degree relatives with psychiatric histories (four patients). Members of the standard surgery cohort were similar, with a history of attempted suicide (two patients), psychiatric treatment for non-gender issues (five patients), and first degree relatives with psychiatric histories (six patients). The early surgery group had surgery approximately 1.75 years prior to the follow-up evaluation. In both groups, cross-dressing began at about age 6.

At baseline, the Bem Sex Role Inventory femininity scores were slightly higher than masculinity scores for both cohorts and were similar to Bem North American female normative scores. The scores did not change in either group over time.

At baseline, the scores for the CCEI individual domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were similar for the cohorts. The total CCEI scores for the two cohorts were consistent with moderate symptoms (Birchnell et al. 1988). Over the two year interval, total CCEI scores increased for standard wait group and approached the relatively severe symptom category. During the same interval, scores dropped into the asymptomatic range for the post-operative patients.

The investigator-designed survey assessed changes in social and sexual activity of the prior two years, but the authors only compared patients in a given cohort to themselves. Though the researchers did not conduct statistical studies to compare the differences between the two cohorts, they did report increased participation in some, but not all, types of social activities such as sports (solo or group), dancing, dining out, visiting pubs, and visiting others. Sexual interest also increased. By contrast, pre-operative patients did not increase their participation in these activities.

2. External Technology Assessments

- a. CMS did not request an external technology assessment (TA) on this issue.
- b. There were no AHRQ reviews on this topic.
- c. There are no Blue Cross/Blue Shield Health Technology Assessments written on this topic within the last three years.

d.

There were two publications in the COCHRANE database, and both were tangentially related. Both noted that there are gaps in the clinical evidence base for gender reassignment surgery.
Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations
Boehmer U. Am J Public Health. 2002; 92: 1125–30.

“Findings supported that LGBT issues have been neglected by public health research and that research unrelated to sexually transmitted diseases is lacking.”

A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. West Midlands Health Technology Assessment Collaboration. Health Technology Assessment Database. Meads, et al., 2009. No.3.

“Further research is needed but must use more sophisticated designs with comparison groups. This systematic review demonstrated that there are so many gaps in knowledge around LGBT health that a wide variety of studies are needed.”

- e. There were no National Institute for Health and Care Excellence (NICE) reviews/guidance documents on this topic.

f.

There was a technology assessment commissioned by the New Zealand Ministry of Health and conducted by New Zealand Health Technology Assessment (NZHTA) (Christchurch School of Medicine and the University of Otago).

*Tech Brief Series: Transgender Re-assignment Surgery Day P. NZHTA Report. February 2002;1(1).
http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf*

The research questions included the following:

1. Are there particular subgroups of people with transsexualism who have met eligibility criteria for gender reassignment surgery (GRS) where evidence of effectiveness of that surgery exists?

2. If there is evidence of effectiveness, what subgroups would benefit from GRS?"

The authors concluded that there was not enough evidence to answer either of the research questions.

3. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) Meeting

CMS did not convene a MEDCAC meeting.

4. Evidence-Based Guidelines

a. American College of Obstetricians and Gynecologists (ACOG)

Though ACOG did not have any evidence-based guidelines on this topic, they did have the following document: Health Care for Transgender Individuals: Committee Opinion
Committee on Health Care for Underserved Women; The American College of Obstetricians and Gynecologists.
Dec 2011, No. 512. Obstet Gynecol. 2011;118:1454-8.

"Questions [on patient visit records]

should be framed in ways that do not make assumptions about gender identity, sexual orientation, or behavior. It is more appropriate for clinicians to ask their patients which terms they prefer. Language should be inclusive, allowing the patient to decide when and what to disclose. The adoption and posting of a nondiscrimination policy can also signal health care providers and patients alike that all persons will be treated with dignity and respect. Assurance of confidentiality can allow for a more open discussion, and confidentiality must be ensured if a patient is being referred to a different health care provider. Training staff to increase their knowledge and sensitivity toward transgender patients will also help facilitate a positive experience for the patient."

b. American Psychiatric Association

Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. Arch Sex Behav. 2012; 41:759-96.

The American Psychiatric Association (APA) was unable to identify any Randomized Controlled Trials (RCTs) regarding mental health issues for transgender individuals.

"There are some level B studies examining satisfaction/regret following sex reassignment (longitudinal follow-up after an intervention, without a control group); however, many of these studies obtained data retrospectively and without a control group (APA level G). Overall, the evidence suggests that sex reassignment is associated with an improved sense of well-being in the majority of cases, and also indicates correlates of satisfaction and regret. No studies have directly compared various levels of mental health screening prior to hormonal and surgical treatments on outcome variables; however, existing studies suggest that comprehensive mental health screening may be successful in identifying those individuals most likely to experience regrets."

[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial.”

[G] Other. Opinion-like essays, case reports, and other reports not categorized above.”

c. Endocrine Society

Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. J Clin Endocrinol Metab. 2009; 94:3132-54.

This guideline primarily addressed hormone management and surveillance for complications of that management. A small section addressed surgery and found the quality of evidence to be low.

“This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low.”

d. World Professional Association for Transgender Health (WPATH)

The WPATH is “an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health.”

WPATH reported, “The standards of care are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person’s gender identity and that person’s sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).”

The WPATH standards of care (SOC) “acknowledge the role of making informed choices and the value of harm-reduction approaches.”

The SOC noted, “For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one’s gender identity);
- Hormone therapy to feminize or masculinize the body;
- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience.”

e. American Psychological Association

Suggested citation: Smith formally published in the American Psychologist. American Psychological Association. (2015): *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People Adopted by the Council of Representatives, August 5 & 7, 2015*. www.apa.org/practice/guidelines/transgender.pdf

"The purpose of the Guidelines for Psychological Practice with Transgender and Gender Nonconforming People (hereafter Guidelines) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice with TGNC people."

"These Guidelines refer to psychological practice (e.g., clinical work, consultation, education, research, training) rather than treatment."

5. Other Reviews

a. Institute of Medicine (IOM)

The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. (Study Sponsor: The National Institutes of Health). Issued March 31, 2011. <http://www.nationalacademies.org/hmd/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and-Transgender-People.aspx>

"To advance understanding of the health needs of all LGBT individuals, researchers need more data about the demographics of these populations, improved methods for collecting and analyzing data, and an increased participation of sexual and gender minorities in research. Building a more solid evidence base for LGBT health concerns will not only benefit LGBT individuals, but also add to the repository of health information we have that pertains to all people."

"Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and

monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adopted to ensure unique characteristics of the target population are properly involved. Involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination.”

b. National Institutes of Health (NIH)

National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013.
http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf

In response to the IOM report, the NIH LGBT research Coordinating Committee noted that most of the health research for this set of populations is “focused in the areas of Behavioral and Social Sciences, HIV (human immunodeficiency virus)/AIDS, Mental Health, and Substance Abuse. Relatively little research has been done in several key health areas for LGBT populations including the impact of smoking on health, depression, suicide, cancer, aging, obesity, and alcoholism.”

6. Pending Clinical Trials

ClinicalTrials.gov

There is one currently listed and recently active trial directed at assessment of the clinical outcomes pertaining to individuals who have had gender reassignment surgery. The study appears to be a continuation of work conducted by investigators cited in the internal technology assessment.

NCT01072825 (Ghent, Belgium sponsor) European Network for the Investigation of Gender Incongruence (ENIGI) is assessing the physical and psychological effects of the hormonal treatment of transgender subjects in two years prior to reassignment surgery and subsequent to surgery. This observational cohort study started in 2010 and is still in progress.

Consistent with the authority at 1862(l)(4) of the Act, CMS consulted with outside experts on the topic of treatment for gender dysphoria and gender reassignment surgery.

Given that the majority of the clinical research was conducted outside of the United States, and some studies either took place in or a suggested continuity-of-care and coordination-of-care were beneficial to health outcomes, we conducted expert interviews with centers across the U.S. that provided some form of specialty-focused or coordinated care for transgender patients. These interviews informed our knowledge about the current healthcare options for transgender people, the qualifications of the professionals involved, and the uniqueness of treatment options. We are very grateful to the organizations that made time to discuss treatment for gender dysphoria with us.

From our discussions with the all of the experts we spoke with, we noted the following practices in some centers: (1) specialized training for all staff about transgender healthcare and transgender cultural issues; (2) use of an intake assessment by either a social worker or health care provider that addressed physical health, mental health, and other life factors such as housing, relationship, and employment status; (3) offering primary care services for transgender people in addition to services related to gender-affirming therapy/treatments; (4) navigators who connected patients with name-change information or other legal needs related to gender; (5) counseling for individuals, groups, and families; (6) an informed-consent model whereby individuals were often referred to as "clients" instead of "patients," and (7) an awareness of depression among transgender people (often measured with tools such as the Adult Outcomes Questionnaire and the Patient Health Questionnaire).

8. Public Comments

We appreciate the thoughtful public comments we received on the proposed decision memorandum. In CMS' experience, public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link: <https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=282&ExpandComments=n#Results>

During the initial comment period, we received 103 comments. Of those, 78% supported coverage of gender reassignment surgery, 15% opposed, and 7% were neutral. The majority of comments supporting coverage were from individuals and advocacy groups.

b. Second Comment Period: June 2, 2016 – July 2, 2016

During the second 30-day public comment period, we received a total of 45 public comments, 7 of which were not posted on the web due to personal health information content. Overall, 82% supported coverage of gender reassignment surgery, 11% opposed, and 7% were neutral or silent in their comment whether they supported or opposed coverage. Half of the comments were submitted by individuals who expressed support for coverage of gender reassignment surgery (51%). We also received comments from physicians, providers, and other health professionals who specialize in healthcare for transgender individuals (17%). We received one comment from a municipality, the San Francisco Department of Public Health. Associations (American Medical Association, American College of Physicians, American Academy of Nursing, American Psychological Association, and LGBT PA Caucus) and advocates (Center for American Progress with many other signatories, Jamison Green & Associates) also submitted comments.

Below is a summary of the comments CMS received. In some instances, commenters identified typographical errors, context missed, and opportunities for CMS to clarify wording and classify articles for ease of reading in the memorandum. As noted earlier, when appropriate and to the extent possible, we updated the decision memorandum to reflect those corrections, improved the context, and clarified the language. In light of public comments, we re-evaluated the evidence and our summaries. We updated our summaries of the studies and clarified the language when appropriate.

1. Contractor Discretion and National Coverage Determination

Comment: Some commenters, including advocates, associations, and providers, supported CMS' decision for MAC contractor discretion/case-by-case determination for gender reassignment surgery. One stakeholder stated, "We agree with the conclusion that a NCD is not warranted at this time."

Response: We appreciate the support and understanding among stakeholders for our proposed decision to have the MACs determine coverage on a case-by-case basis. We have clarified in this final decision memorandum that

Comment: Some commenters cautioned that CMS' choice to not issue a NCD at this time must not be interpreted as a national non-coverage determination or used in any way to inappropriately restrict access to coverage for transgender Medicare beneficiaries or other transgender individuals. Multiple commenters indicated their disappointment that CMS did not propose a National Coverage Determination (NCD) and, instead, chose to continue to have local MACs make the coverage decisions on a case-by-case basis. Commenters stated this could result in variability in coverage.

Response: We appreciate the comments. We are not issuing a NCD at this time because the available evidence for gender reassignment surgery provides limited data on specific health outcomes and the characteristics of specific patient populations that might benefit from surgery. In the absence of a NCD, the MAC's use the same statutory authority as NCDs, section 1862(a)(1)(A) of the Social Security Act (the Act). Under section 1862(a)(1)(A) an item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. While CMS did not have enough evidence to issue a NCD, we believe the MACs will be able to make appropriate coverage decisions on a case-by-case basis taking into account individual characteristics of the Medicare beneficiary.

Comment: Some commenters sought a NCD that would establish guidelines for coverage and include elements such as a prescribed set of surgeries and a shared decision making element.

Response: For the reasons stated above, we are not issuing a NCD at this time and, therefore, are not establishing specific gender reassignment surgery coverage guidelines for the Medicare program. We generally agree that shared decision-making is a fundamental approach to patient-centered health care decisions and strongly encourage providers to use these types of evidence based decision aids. We have not found a shared decision aid on GRS and encourage the development of this necessary element to conduct formal shared-decision making.

Comment: Some commenters expressed concern that there is a misunderstanding of transgender individuals as having a disorder or being abnormal. Some commenters indicated a history of bias and discrimination within society as a whole that has occurred when transgender individuals have sought health care services from the medical community. Some commenters are concerned that the decision not to make a NCD will subject individuals seeking these services to corporate bias by Medicare contractors.

Response: We acknowledge the public comments and that there has been a transformation in the treatment of individuals with gender dysphoria over time. We acknowledge that gender dysphoria is a recognized condition in the Diagnostic and Statistical Manual of Mental Disorders (DSM) condition. With respect to the concern about potential bias by Medicare contractors, we have no reason to expect that the judgments made on specific claims will be influenced by an overriding bias, hostility to patients with gender dysphoria, or discrimination. Moreover, the Medicare statute and our regulations provide a mechanism to appeal an adverse initial decision if a claim is denied and those rights may include the opportunity for judicial review. We believe the Medicare appeals process would provide an opportunity to correct any adverse decision that was perceived to have been influenced by bias.

Comment: Commenters mentioned the cost of gender reassignment surgery could influence MAC decision making.

Response: The decisions on whether to cover gender reassignment surgery in a particular case are made on the basis of the statutory language in section 1862 of the Social Security Act that establish exclusions from coverage and would not depend on the cost of the procedure.

2. Coverage with Evidence Development and Research

Comment: In our proposed decision memorandum, we specifically invited comments on whether a study could be developed that would support coverage with evidence development (CED). One organization commented, "We strongly caution against instituting a CED protocol." Commenters were opposed to coverage limited in clinical trials, suggesting that such coverage would restrict access to care. Several commenters provided suggested topics for clinical research studies for the transgender population. For example, one commenter suggested a study of non-surgical treatment for transgender children prior to puberty.

Response: While we appreciate the comments supporting further research, in general, for gender reassignment surgery, we agree that CED is not the appropriate coverage pathway at this time. While CED is an important mechanism to support research and has the potential to be used to help address gaps in the current evidence, we are not aware of any available, appropriate studies, ongoing or in development, on gender reassignment surgery for individuals with gender dysphoria that could be used to support a CED decision.

3. Gender Reassignment Surgery as Treatment

Comment: One group of commenters requested that CMS consider that, “The established medical consensus is that GRS is a safe, effective, and medically necessary treatment for many individuals with gender dysphoria, and for some individuals with severe dysphoria, it is the only effective treatment.”

Response: We acknowledge that GRS may be a reasonable and necessary service for certain beneficiaries with gender dysphoria. The current scientific information is not complete for CMS to make a NCD that identifies the precise patient population for whom the service would be reasonable and necessary.

4. Physician Recommendations

Comment: Several commenters stated that gender reassignment surgery should be covered as long as it was determined to be necessary, or medically necessary by a beneficiary’s physician.

Response: Physician recommendation is one of many potential factors that the local MAC may consider when determining whether the documentation is sufficient to pay a claim.

5. WPATH Standards of Care

Comment: Several commenters suggested that CMS should recommend the WPATH Standards of Care (WPATH) as the controlling guideline for gender reassignment surgery. They asserted it could satisfy Medicare’s reasonable and necessary criteria for determining coverage on a case-by-case basis.

Response: Based on our review of the evidence and conversations with the experts and patient advocates, we are aware some providers consult the WPATH Standards of Care, while others have created their own criteria and requirements for surgery, which they think best suit the needs of their patients. As such, and given that WPATH acknowledges the guidelines should be flexible, we are not in the position to endorse exclusive use of WPATH for coverage. The MACs, Medicare Advantage plans, and Medicare providers can use clinical guidelines they determine useful to inform their determination of whether an item or service is reasonable and necessary. When making this determination, local MACs may take into account physician’s recommendations, the individual’s

6. Scope of the NCA Request

Comment: One commenter stated that CMS did not address the full scope of the NCA request.

Response: The formal request for a NCD is publicly available on our tracking sheet. (<https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id282.pdf>) The letter did not explicitly seek a national coverage determination related to counseling or hormone therapies, but focused on surgical remedies. CMS is aware that beneficiaries with gender dysphoria use a variety of therapies.

Comment: Other commenters stated the scope of the proposed decision is unnecessarily broad because it discussed therapies other than surgery. They suggested this discussion could lead to the unintended consequence of restricting access to those services for transgender Medicare beneficiaries and other transgender individuals.

Response: As we noted in our proposed decision, our decision focused only on gender reassignment surgery. In the course of reviewing studies related to those surgeries, occasionally authors discussed other therapies that were mentioned in our summaries of the evidence. To the extent possible, we have modified our decision to eliminate the discussion of other therapies which were not fully evaluated in this NCA.

7. NCA Question

Comment: Some commenters expressed concern about the phrasing of the question in this NCA.

Response: The phrasing of the research question is consistent with most NCAs and we believe it is appropriate.

8. Evidence Summary and Analysis

Comment: Several commenters disagreed with our summary of the clinical evidence and analysis. A few commenters contended that the overall tone of the review was not neutral and seemed biased or flawed. One commenter noted that the Barrett publication was available on the Internet.

Response: We appreciate the comments that identified technical errors, and we made the necessary revisions to this document. However, we disagree with the contention that our evidence review was not neutral and seemed biased or flawed. We believe that the summary and analysis of the clinical evidence are objective. As with previous NCAs, our review of the evidence was rigorous and methodical. Additionally, we reviewed the Barrett publication, but it did not meet our inclusion criteria to be included in the Evidence section.

9. Evidence Review with Transgender Experts

Comment: Several commenters requested that CMS re-review the clinical evidence discussed in the proposed decision memorandum with outside experts in the field of transgender health and transition/gender reassignment-related surgeries. Several offered the expertise within their organization to assist in this effort.

Response: We appreciate these comments and the transgender health community's willingness to participate. For this NCA we discussed gender reassignment surgery protocols with experts, primarily in coordinated care settings. Additionally, the public comment periods provide opportunities for expert stakeholder input. According to our process for all NCAs, we do not jointly review evidence with external stakeholders but have carefully reviewed the very detailed comments submitted by a number of outside experts in transgender health care.

10. Previous Non-Coverage NCD

Response: CMS does not directly conduct clinical studies or pay for research grants. Some medical services are non-covered by Medicare; however, national non-coverage does not preclude research via a number of avenues and other funding entities such as the National Institutes of Health. In this instance, the previous NCD did not preclude interested parties from funding research for gender reassignment surgery that could have been generalizable to the Medicare population.

11. How the Medicare Population Differs from the General Population

Comment: One commenter questioned how the Medicare population differed from the general population, and why any differences would be important in our decision-making.

Response: The Medicare population is different from the general population in age (65 years and older) and/or disability as defined by the Social Security Administration. Due to the biology of aging, older adults may respond to health care treatments differently than younger adults. These differences can be due to, for example, multiple health conditions or co-morbidities, longer duration needed for healing, metabolic variances, and impact of reduced mobility. All of these factors can impact health outcomes. The disabled Medicare population, who are younger than age 65, is different from the general population and typical study populations due to the presence of the causes of disability such as psychiatric disorders, musculoskeletal health issues, and cardiovascular issues.

12. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

Comment: One commenter suggested CMS should have convened a MEDCAC for this topic.

Response: We appreciate the comment. Given the limited evidence, we did not believe a MEDCAC was warranted according to our guidance document entitled "Factors CMS Considers in Referring Topics to the Medicare Evidence Development & Coverage Advisory Committee" (<https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/MEDCAC.html>).

13. §1557 of the Affordable Care Act (ACA)

Comment: Some commenters asserted that by not explicitly covering gender reassignment surgery at the national level, CMS was discriminating against transgender beneficiaries in conflict with Section 1557 of the Accountable Care Act (ACA).

Response: This decision does not affect the independent obligation of covered entities, including the Medicare program and MACs, to comply with Section 1557 in making individual coverage decisions. In accordance with Section 1557, MACs will apply neutral nondiscriminatory criteria when making case-by-case coverage determinations related to gender reassignment surgery.

14. Medicaid

Comment: Some commenters observed that some states cover gender reassignment surgery through Medicaid or require commercial insurers operating in the state to cover the surgery.

Response: We appreciate the information about Medicaid and state requirements; however, State decisions are separate from Medicare coverage determinations. We make evidence-based determinations based on our statutory standards and processes.

15. Commercial Insurers

Comment: In several instances, commenters told us that the healthcare industry looks to CMS coverage determinations to guide commercial policy coverage.

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Response: CMS makes evidence-based national coverage determinations based on our statutory standards and processes as defined in the Social Security Act, which may not be the same standards that are used in commercial insurance policies or by other health care programs. In addition as noted above, the Medicare population is different (e.g., Medicare covers 95% of adults 65 and older) than the typical population under commercial insurers. We do not issue coverage decisions to drive policy for other health organizations' coverage in one way or the other.

16. Healthcare for Transgender Individuals

Comment: Numerous professional associations wrote to CMS to explain their support for access to healthcare for transgender individuals.

Response: CMS recognizes that transgender beneficiaries have specific healthcare needs. Many health care treatments are available. We encourage all beneficiaries to utilize their Medicare benefits to help them achieve their best health.

17. Intended Use of the Decision Memorandum

Comment: Several commenters expressed concern that the analysis provided in the proposed and final decision memorandums may be used by individuals, entities, or payers for purposes unrelated to Medicare such as denial of coverage for transgender-related surgeries.

Response: The purpose of the decision memoranda is to memorialize CMS' analysis of the evidence, provide responses to the public comments received, and to make available the clinical evidence and other data used in making our decision consistent with our obligations under the § 1862 of the Act. The NCD process is open and transparent and our decisions are publicly available. Congress requires that we provide a clear statement of the basis for our determinations. The decision memoranda are an important part of the record of the NCD. Our focus is the Medicare population which, as noted above, is different than the general population in a number of ways. Other entities may conduct separate evidence reviews and analyses that are suited for their specific populations.

Comment: A few commenters stated that without Medicare coverage, surgery is difficult to afford and there may be a risk of negative consequences for the individual. One commenter suggested that CMS should consider prior-authorization for these surgeries.

Response: CMS is aware that paying out-of-pocket for medical care is a strain on a beneficiary's finances. We are also aware of beneficiaries' hesitancy to undergo surgery prior to knowing whether or not Medicare will pay the claim. Gender reassignment surgeries are not the only procedures whereby payment is not determined until after the provider submits the claim to Medicare. Importantly, documentation for the claims need to be explicit about what procedures were performed and include the appropriate information in the documentation to justify using the code or codes for surgery. Of note, CMS has claims data that indicate Medicare has paid for gender reassignment surgeries in the recent past. Determining which services are designated for prior-authorization is outside of the scope of the NCA process.

19. Surgical Risks and Benefits

Comment: A number of commenters conveyed the benefits of gender reassignment surgery, while other commenters expressed concern that gender reassignment surgery was harmful.

Response: We appreciate these comments.

20. Expenditure of Federal Funds

Comment: Some commenters opposed spending Medicare program funds on gender reassignment surgery for a variety of reasons. For example, some commenters believe it is an "elective" procedure. Other commenters suggested that funds should first be spent on other priorities such as durable medical equipment (DME) or mobility items such as power chairs; increasing reimbursement to providers; or that spending should be limited to the proportion to the transgender adult population in the Medicare program.

Response: The purpose of this NCA is to determine whether or not CMS should issue a NCD to cover surgery for patients who have gender dysphoria. NCAs do not establish payment amounts or spending priorities and, therefore, these comments are outside the scope of this consideration.

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under § 1862(l)(6) of the Act. In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage.

Moreover, in most circumstances, the item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)). The Supreme Court has recognized that “[t]he Secretary’s decision as to whether a particular medical service is ‘reasonable and necessary’ and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions.” *Heckler v. Ringer*, 466 U.S. 602, 617 (1984). See also, 78 Fed. Reg. 48,164, 48,165 (August 7, 2013)

When making national coverage determinations, we consider whether the evidence is relevant to the Medicare beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully consider the demographic characteristics and comorbidities of study participants as well as the provider training and experience. This section provides an analysis of the evidence, which included the published medical literature and guidelines pertaining to gender dysphoria, that we considered during our review to answer the question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

CMS carefully considered all the studies listed in this decision memorandum to determine whether they answered the question posed in this NCA. While there appears to be many publications regarding gender reassignment surgery, it became clear that many of the publications did not meet our inclusion/exclusion criteria as explained earlier in the decision memorandum.

A. Quality of the Studies Reviewed

Overall, the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding (a situation where the association between the intervention and outcome is influenced by another factor such as a co-intervention), small sample sizes, lack of validated assessment tools, and considerable lost to follow-up (Appendices C and F). The impact of a specific therapeutic intervention can be difficult to determine when there are multiple serial treatments such as psychotherapy, hormone treatment and surgery. To reduce confounding, outcome assessment just prior to and after surgery such as in a longitudinal study would be helpful. The objective endpoints included psychiatric treatment, attempted suicide, requests for surgical reversal, morbidity (direct and indirect adverse events), and mortality (Appendix F). CMS agrees with the utility of these objective endpoints. Quality of life, while important, is more difficult to measure objectively (Appendix E).

Of the 33 studies reviewed, published results were conflicting – some were positive; others were negative. Collectively, the evidence is inconclusive for the Medicare population. The majority of studies were non-longitudinal, exploratory type studies (i.e., in a preliminary state of investigation or hypothesis generating), or did not include concurrent controls or testing prior to and after surgery. Several reported positive results but the potential issues noted above reduced strength and confidence. After careful assessment, we identified six studies that could provide useful information (Figure 1). Of these, the four best designed and conducted studies that assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies did not demonstrate clinically significant changes or differences in psychometric test results after GRS. (Heylens et al., 2014; Ruppín, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008) (Appendix C Panel A and Appendix G.)

Two studies (three articles) assessed functional endpoints (request for surgical reassignment reversal and morbidity/mortality) (Dhejne et al., 2011; Dhejne et al., 2014 along with Landén et al., 1998) (Figure 1 and Appendix C, Panel A and Appendix G). Although the data are observational, they are robust because the Swedish national database is comprehensive (including all patients for which the government had paid for surgical services) and is notable for uniform criteria to qualify for treatment and financial coverage by the government. Dhejne et al. (2014) and Landén et al. (1998) reported cumulative rates of requests for surgical reassignment reversal or change in legal status of 3.3% while Dhejne et al. (2014) reported 2.2%. The authors indicated that the later updated calculation had the potential to be an underestimate because the most recent surgical cohorts were larger in size and had shorter periods of follow-up.

Dhejne et al., (2011) tracked all patients who had undergone reassignment surgery (mean age 35.1 years) over a 30 year interval and compared them to 6,480 matched controls. The study identified increased mortality and psychiatric hospitalization compared to the matched controls. The mortality was primarily due to completed suicides (19.1-fold greater than in control Swedes), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. We note, mortality from this patient population did not become apparent until

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after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in controls even after adjustment for psychiatric disease (10). The risk of completed suicide was greater in the female patients regardless of the gender of the control. Further, we cannot exclude therapeutic interventions as a cause of the observed excess morbidity and mortality. The study, however, was not constructed to assess the impact of gender reassignment surgery *per se*.

We believe at minimum study designs should have a pre-test/post-test longitudinal design accompanied by characterization of all patients lost to follow-up over the entire treatment series as well as those patients who did not complete questionnaires, and the use of psychometric quality-of-life tools which are well validated with linkage to "hard" (objective) patient outcomes in this particular patient population (Trentacosti 2007, PRO 2009) (Appendices C and D).

Patient Care

Clinical evidentiary questions regarding the care of patients with gender dysphoria remain. Many of the publications focused on aspects of surgical technique as opposed to long-term patient outcomes. The specific type(s) of gender/sex reassignment surgery (e.g., genital, non-genital) that could improve health outcomes in adults remain(s) uncertain because most studies included patients who had undertaken one or more of a spectrum of surgical procedures or did not define the specific types of surgical procedures under study. Furthermore, surgical techniques have changed significantly over the last 60 years and may not reflect current practice (Bjerrome Ahlin et al., 2014; Doornaert, 2011; Green, 1998; Pauly, 1968; Selvaggi et al., 2007; Selvaggi, Bellringer, 2011; Tugnet et al., 2007; Doornaert, 2011).

The WPATH care recommendations present a general framework and guidance on the care of the transgender individual. The standards of care are often cited by entities that perform gender reassignment surgery. WPATH notes, "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria." Appendix D in the WPATH Standards of Care briefly describes their evidence base and acknowledges the historical problems with evidentiary standards, the preponderance of retrospective data, and the confounding impact of multiple interventions, specifically distinguishing the impact of hormone therapy from surgical intervention.

Additionally, CMS met with several stakeholders and conducted several interviews with centers that focus on healthcare for transgender individuals in the U.S. Primary care rather than gender reassignment surgery was often the main focus. Few of the U.S.-based reassignment surgeons we could identify work as part of an integrated practice, and few provide the most complex procedures.

CMS reviewed psychometric endpoints because gender dysphoria (inclusive of prior nomenclature) describes an incongruence between the gender assigned at birth and the gender(s) with which the person identifies.

The psychometric tools used to assess outcomes have limitations. Most instruments that were specific for gender dysphoria were designed by the investigators themselves or by other investigators within the field using limited populations and lacked well documented test characterization. (Appendices E and F) By contrast, test instruments with validation in large populations were non-specific and lacked validation in the gender dysphoric patient populations. (Appendices E and F). In addition, the presentation of psychometric results must be accompanied by enough information about the test itself to permit adequate interpretation of test results. The relevant diagnostic cut-points for scores and changes in scores that are clinically significant should also be scientifically delineated for interpretation.

Generalizability

It is difficult to generalize these study results to the current Medicare population. Many of the studies are old given they were conducted more than 10 years ago. Most of these studies were conducted outside of the U.S. in very different medical systems for treatment and follow-up. Many of the programs were single-site centers without replication elsewhere. The study populations were young and without significant physical or psychiatric co-morbidity (Appendix D). As noted earlier, psychiatric co-morbidity may portend poor outcomes (Asscheman et al., 2011; Landén et al., 1998).

Knowledge Gaps

This patient population faces complex and unique challenges. The medical science in this area is evolving. This review has identified gaps in the evidentiary base as well as recommendations for good study designs. The Institute of Medicine, the National Institutes of Health, and others also identified many of the gaps in the data. (Boehmer, 2002; HHS-HP, 2011; IOM, 2011; Kreukels-ENIGI, 2012; Lancet, 2011; Murad et al., 2010; NIH-LGBT, 2013) The current or completed studies listed in ClinicalTrials.gov are not structured to assess these gaps. These gaps have been delineated as they represent areas in which patient care can be optimized and are opportunities for much needed research.

Four studies included information on racial or ethnic background. The participants in the three U.S. based studies were predominantly Caucasian (Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006). All of the participants in the single Asian study were Chinese (Tsoi, 1993). Additional research is needed in this area.

C. Summary

Based on an extensive assessment of the clinical evidence as described above, there is not enough high quality evidence to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively.

The knowledge on gender reassignment surgery for individuals with gender dysphoria is evolving. Much of the available research has been conducted in highly vetted patients at select care programs integrating psychotherapy, endocrinology, and various surgical disciplines. Additional research of contemporary practice is needed. To assess long-term quality of life and other psychometric outcomes, it will be necessary to develop and validate standardized psychometric tools in patients with gender dysphoria. Further, patient preference is an important aspect of any treatment. As study designs are completed, it is important to include patient-centered outcomes.

Because CMS is mindful of the unique and complex needs of this patient population and because CMS seeks sound data to guide proper care of the Medicare subset of this patient population, CMS strongly encourages robust clinical studies with adequate patient protections that will fill the evidence gaps delineated in this decision memorandum. As the Institute of Medicine (IOM, 2011) importantly noted: "Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

IX. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery. App. 797

surgery on a case-by-case basis. We have received a complete, formal request to make a national coverage determination on surgical treatments for gender identity disorders (GID), Page 802 of 919 Page 1268 Case 7:16-cv-00108-E Document 26 Filed 10/21/16 Page 1268 The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination on whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual’s specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery would be reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination relating to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

A. Appendix A

Diagnostic & Statistical Manual of Mental Disorders (DSM) Criteria for Disorders of Gender Identity since 1980

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III 1980				Further characterization of sexual orientation App 598

DSM Version	Condition Name	Criteria	Criteria	Comments
Case 7:16-cv-00108-O Chapter: <i>Psychosexual Disorders</i>	Trans-sexualism 302.5x [Gender Identity Disorder of Child-hood (302.6)]	Required A (cross-gender identification) and B (aversion to one's natal gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	Sense of discomfort and inappropriateness about one's anatomic sex. Wish to be rid of one's own genitals and to live as a member of the other sex. The disturbance has been continuous (not limited to periods of stress) for at least 2 years.	Distinguished from Atypical Gender Identity Disorder 302.85
DSM III-Revised 1987 <i>TS classified as an Axis II dx (personality disorders and mental retardation) in a different chapter. GID included under Disorders Usually First Evident in Infancy, Childhood, Adolescence</i>	Trans-sexualism (TS) (302.50) [GID of C]	Required A and B criteria	Persistent discomfort and sense of inappropriateness about one's assigned sex. Persistent preoccupation for at least 2 years with getting rid of one's 1° and 2° sex characteristics and acquiring the sex characteristics of the other sex. Has reached puberty	Further characterization by sexual orientation Distinguished from Gender Identity Disorder of Adolescence or Adulthood, Non-trans-sexual Type •e.g., cross-dressing not for the purposes of sexual excitement Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions Gender Identity Disorder Not Otherwise Specified 302.85 •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
	GID of adulthood , non-trans-sexual type, added			
DSM IV 1994 Chapter: <i>Sexual & Gender Identity Disorders</i>	Gender Identity Disorder in Adolescents and Adults (302.85) (Separate criteria & code for children, but same name)	Required A and B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., Stated desire to be another sex •e.g., Desire to live or be treated as a member of the other sex •e.g., conviction that he/she has the typical feelings and reactions of the other sex •e.g., frequent passing as the other sex Persistent discomfort with his/her sex or sense of inappropriateness in the gender role of that sex. •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1° and 2° sex characteristics &/or acquiring sexual traits of the other sex	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex

DSM Version	Condition Name	Criteria	Criteria	Comments
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DSM IV-Revised 2000 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder (Term transsexual-ism eliminated)	Required A & B criteria Dx excluded by physical intersex condition	<ul style="list-style-type: none"> •Clinically significant distress or impairment in social, occupational, or other important areas of functioning <p>Cross-gender identification</p> <ul style="list-style-type: none"> •e.g., stated desire to be the other sex •e.g., desire to live or be treated as the other sex •e.g., conviction that he/she has the typical feelings & reactions of the other sex •e.g., frequent passing as the other sex <p>Persistent discomfort with his or her sex OR sense of inappropriateness in the gender role of that sex</p> <ul style="list-style-type: none"> •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1^o and 2^o sex characteristics &/or acquiring sexual traits of the other sex <p>Clinically significant distress or impairment in social, occupational, or other important areas of functioning</p>	<p>Outcome may depend on time of onset</p> <p>Further characterization by sexual orientation</p> <p>Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6</p> <ul style="list-style-type: none"> •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM V 2013 <i>Separate Chapter from Sexual Dysfunctions & Paraphilic Disorders</i>	Gender Dysphoria (302.85)	<p>Gender nonconformity itself not considered to be a mental disorder</p> <p>The dysphoria associated with the gender incongruence is</p> <p>Eliminates A & B criteria</p> <p>Considers gender incongruence to be a spectrum</p> <p>Considers intersex/ "disorders of sex development" to be a subsidiary and not exclusionary to dx of GD</p>	<ul style="list-style-type: none"> •Marked discordance between natal 1^o and 2^o sex characteristics* and experienced/expressed gender •Conviction that he/she has the typical feelings & reactions of the other sex (or some alternative gender) •Marked desire to be the other sex (or some alternative gender) •Marked desire to be treated as the other sex (or some alternative gender) •Marked desire to be rid of natal 1^o and 2^o sex characteristics** •Marked desire to acquire 1^o and 2^o sex characteristics of the other sex (or some alternative gender) <p>Clinically significant distress or impairment in social, occupational, or other important areas of functioning</p> <p>* or in young adolescents, the anticipated 2^o sex characteristics</p>	<p>Includes diagnosis for post transition state to permit continued treatment access</p> <p>Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity syndromes</p>

DSM Version	Condition Name	Criteria	Criteria	Comments
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			<p>** or in young adolescents, prevent the development of the anticipated 2° sex characteristics</p> <p>≥ 6 month marked discordance between natal gender & experienced/expressed gender as demonstrated by ≥ 6 criteria:</p> <ul style="list-style-type: none"> •Strong desire to be of the other gender or an insistence that one is of another gender. •Strong preference for cross-gender roles in make-believe play. •Strong preference for the toys, games, or activities of the other gender. •Strong preference for playmates of the other gender. •In boys, strong preference for cross-dressing; in girls, strong preference for wearing masculine clothing •In boys, rejection of masculine toys, games, activities, avoidance of rough and tumble play; in girls, rejection of feminine toys, games, and activities. 	
	Unspecified Gender Dysphoria (302.6) (F64.9)		This category applies to presentations in which sx c/w gender dysphoria that cause clinically significant distress or impairment, but do not meet the full criteria for gender dysphoria & the reason for not meeting the criteria is not provided.	
	Specified Gender Dysphoria 302.6 (F64.8)		If the reason that the presentation does not meet the full criteria is provided then this dx should be used	

C/W=consistent with Dx=diagnosis GD=gender dysphoria Sx=symptoms TS=transsexual 1°=primary 2°=secondary

B. Appendix B

1. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention study.

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology’s benefits and risk of harm to Medicare beneficiaries.

Appendix C

Patient Population: Enrolled & Treated with Sex Reassignment Surgery Loss of Patients & Missing Data

Panel A (Controlled Studies)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Dhejne 2011	Longitudinal Controlled	804 w GD	324	324 (100%)	-
Dhejne 2014 Landén	Longitudinal for test variable Controlled	767 applied for SRS 25 applications denied. 61 not granted full legal status 15 formal applications for surgical reversal	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper
Heylens	Longitudinal Controlled	90 applicants for SRS 33 excluded 11 later excluded had not yet received SRS by study close.	57 (46)	46 (80.7%) Only those w SRS evaluated	Psycho-social survey missing data for 3 at baseline & 4 after SRS.

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
					SCL90 not completed by 1 at baseline, 10 after hormone tx, & 4 after SRS missing data for another 1.1% to 11.1%.
Kockott	Longitudinal Controlled	80 applicants for SRS 21 excluded	59	32 (54.2%) went to surgery	1 preoperative patient was later excluded b/c lived completely in aspired gender w/o SRS. Questions on financial sufficiency not answered by 1 surgical pt. Questions on sexual satisfaction & gender contentment not answered by 1 & 2 patients awaiting surgery respectively.
Mate-Kole 1990	Longitudinal Controlled	40 sequential patients of accepted patients. The number in the available patient pool was not specified.	40	20 (50%) went to surgery	-
Meyer	Longitudinal Controlled	Recruitment pool: 100 50 were excluded.	50	15 (30%) had undergone surgery 14 (28%) underwent surgery later	The assessments of all were complete
Rakic	Longitudinal Controlled	92 were evaluated 54 were excluded from surgery 2 post SRS were lost to follow-up 2 post SRS were excluded for being in the peri-operative period	32	32 (100%)	Questionnaire completed by all.
Ruppin	Longitudinal Controlled	The number in the available patient pool was not specified. 140 received recruitment letters. 69 were excluded	71	69 (97.2%)	The SCL-90, BSRI, FPI-R, & IPP tests were not completed by 9, 34, 13, & 16 respectively. Questions about romantic relationships, sexual relationships, friendships, & family relationships were not answered by 1, 3, 2, & 23 respectively. Questions regarding gender security & regret & were not answered by 1 & 2 respectively.
Smith	Longitudinal Controlled	The number in the available adult patient pool was not specified.	162	162 (100%)	

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Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
		325 adult & adolescent applicants for SRS were recruited. 103 were excluded from additional tx			36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete various post-SRS tests.
Udeze Megeri	Longitudinal Controlled	International patient w GD 546 & post SRS 318. 40 M to F subjects were prospectively selected.	40	40 (100%)	-
Ainsworth	Internet/convention Survey Cross-sectional Controlled	Number of incomplete questionnaires not reported	247	72 (29.1%) 75 (30.6%) facial 147 (59.5%) had received neither facial nor reassignment surgery	-
Beatrice	Cross-sectional Controlled	14 excluded for demographic matching reasons	40	10 (25%)	The assessments were completed by all
Haraldsen	Cross-sectional Controlled	Recruitment pool: 99	86	59 (68.6%)	-
Kraemer	Cross-sectional Controlled	The number in the available patient pool was not specified.	45	22 (48.9%)	-
Kuhn	Cross-sectional Controlled	The number in the available patient pool was not specified.	75	55 (73.3%)	-
Mate-Kole 1988	Cross-sectional Controlled	150 in 3 cohorts. Matched on select traits. The number in the available patient pool was not specified.	150	50 (66.7%)	-
Wolfradt	Cross-sectional Controlled	The number in the available patient pool was not specified.	90	30 (33.3%)	-

Panel B (Surgical Series: No Concurrent Controls)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Blanchard et al.	Cross-sectional Control: Normative test data	294 clinic patients w GD had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded	79	79(100%)	-
Weyers et al.	Cross-sectional Control: Normative test data	>300 M to F patients had undergone GRS 70 eligible patients recruited 20 excluded	50	50 (100%)	SF-26 not completed by 1
Wierckx et al.	Cross-sectional except for recall questions Control: Normative test data	79 F to M patients had undergone GRS & were recruited.	49	49 (100%)	SF-36 test not completed by 2. App. 807

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Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
		3 additional non-clinic patients were recruited by other patients. 32 excluded initially; 1 later.			Questions regarding sexual re-lationship, sex function, & surgical satisfaction were answered by as few as 27, 28, 32 respectively.
Eldh et al.	Cross-sectional except for 1 variable Control: Self for 1 variable-employment	136 were identified. 46 excluded	90	90 (100%)	Questions regarding gender iden-tity, sex life, acceptance, & overall satisfaction were not answered by 13, 14, 14 & 16 respectively. Employment data missing for 11.
Hess et al.	Cross-sectional No control	254 consecutive eligible patients post GRS identified & sent surveys. 135 excluded.	119	119 (100%)	Questions regarding the esthetics, functional, and social outcomes of GRS were not answered by 16 to 28 patients.
Lawrence	Cross-sectional No control	727 eligible patients were recruited. 495 were excluded	232	232 (100%)	-
Salvador et al.	Cross-sectional No control	243 had enrolled in the clinic 82 completed GRS 69 eligible patients were identified. 17 excluded.	52	52 (100%)	-
Tsoi	Cross-sectional No control	The number in the available patient pool was not specified.	81	81 (100%)	-

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Gómez-Gil et al. 2012	Cross-sectional No direct control: Analysis of variance	200 consecutive patients were recruited. 13 declined participation or were excluded for incomplete questionnaires.	187	79 (42.2%)	See prior box.
Hepp et al.	Cross-sectional No direct control: Analysis of variance	The number in the available patient pool was not specified.	31	7 (22.6%)	HADS test not completed by 1
Motmans et al.	Cross-sectional No direct control: Analysis of variance & regression	255 with GD were identified. 77 were excluded.	148 (140)	Not clearly stated. At least 103 underwent some form of GRS.	8 later excluded for incomplete SF-36 tests.

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Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
					37 w recent GRS or hormone initiation were excluded from analysis of SF-36 results ¹⁰³ .
Newfield et al.	Internet survey Cross-sectional No direct control: Analysis of variance	Number of incomplete questionnaires not reported 446 respondents; 384 U.S. respondents 62 non-U.S. respondents excluded from SF-36 test results 8 U.S. respondents excluded	376 (U.S.)	139 to 150 (37.0-39.9%) in U.S.	-
Gomez-Gil et al. 2014	Cross-sectional No direct control: Analysis w regression	The number in the available patient pool was not specified. 277 were recruited. 25 excluded	252(193)	80 (41.4%) non-genital surgery	59 were excluded for incomplete questionnaires. See prior box.
Asscherman	Longitudinal No analysis by tx status	The number in the available patient pool was not specified.	1331	1177 (88.4%)	-
Johansson et al.	Cross-sectional except for 1 variable No analysis by tx status except for 1 question	60 eligible patients 18 excluded.	42	32 (76.2% of enrolled & 53.3% of eligible) (genital surgery)	-
Leinung et al.	Cross-sectional No analysis by tx status	242 total clinic patients	242	91 (37.6%)	Employment status data missing for 81 of all patients

*Data obtained via a survey on a website and distributed at a conference

B/C=because

BSRI=Bem Sex Role Inventory

F=Female

FP-R=Freiberg Personality Inventory

GD=Gender dysphoria

GID=Gender identity disorder

HADS=Hospital Anxiety & Depression Scale

IPP=Inventory of Interpersonal Problems

M=Male

NA=Not applicable

SCL-90=Symptom Checklist-90

SF-36=Short Form 36

GRS=Sex reassignment surgery

Tx=Treatment

W/o=without

Appendix D

Panel A (Controlled Studies)

Author	Age (years; mean, S.D., range)	Gender	Race
Ainsworth	Only reassignment surgery: 50 (no S.D.) Only facial surgery: 51 (no S.D.) Both types of surgery: 49 (no S.D.) Neither surgery: 46 (no S.D.)	247 M to F	-
Beatrice	Pre-SRS M to F: 32.5 (27-42), Post-SRS: 35.1 (30-43)	20 M to F plus 20 M controls	100% Caucasian
Dehjne 2011	Post-SRS: all 35.1±9.7 (20-69), F to M 33.3+8.7 (20-62), M to F 36.3+10.1(21-69)	133 (41.0%) F to M, 191 (59.0%) M to F; ratio 1:1.4	-
Dhejne 2014 Landén	F to M SRS cohort: median age 27 M to F SRS cohort: median age 32 F to M applicants for reversal: median age 22 M to F applicants for reversal: median age 35	767 applicants for legal/surgical reassignment 289 (37.7%) F to M, 478 (62.3%) M to F; ratio 1:1.6 681 post SRS & legal change 252 (37.0%) F to M, 429 (63.0%) M to F; ratio 1:1.7 15 applicants for reversal 5 (33.3%) F to M, 10 (66.7%) M to F; ratio 1:2	-
Haraldsen	Pre-SRS & Post-SRS: F to M 34±9.5, F to M 33.3±10.0 Post-SRS cohort reportedly older. No direct data provided.	Pre & Post SRS 35 (40.7%) F to M, 51 (59.3%) M to F; ratio 1:1.5	-
Heylens	-	11 (19.3% of 57) F to M, 46 (80.7%); ratio 1:4.2 (80.7% underwent surgery)	-
Kockott	Pre-SRS (continued wish for surgery): 31.7±10.2 Post-SRS: 35.5±13.1	Pre-SRS (continued wish for surgery) 3 (25%) F to M, 9 (75%) M to F; ratio 1:3 Post SRS: 14 (43.8%) F to M, 18 (56.2%) M to F; ratio 1:1.3	-
Kraemer	Pre-SRS: 33.0±11.3, Post-SRS: 38.2±9.0	Pre-SRS 7 F to M (30.4%), 16 M to F (69.6%); ratio 1:2.3 Post-SRS 8 F to M (36.4%), 14 M to F (63.6%); ratio 1:1.8	-
Kuhn	All post SRS: median (range): 51 (39-62) (long-term follow-up)	3 (5.4%) F to M, 52 (94.5%) M to F; ratio 1:17.3.	-
Mate-Kole 1988	Initial evaluation: 34, Pre-SRS: 35, Post-SRS: 37	150 M to F	-
Mate-Kole 1990	Early & Usual wait SRS: 32.5 years (21-53)	40 M to F	-
Meyer	Pre-SRS: 26.7 Delayed, but completed SRS: 30.9 Post-SRS: 30.1	Pre-SRS: 5 (23.8%) F to M, 16 (76.2%) M to F; ratio 1:3.2 Delayed, but completed SRS: 1 (7.1%) F to M, 13 (92.9%) M to F; ratio 1:13 Post-SRS: 4 (26.7%) F to M, 11 (73.3%) M to F; ratio 1:2.8	86% Caucasian
Rakic	All: 26.8±6.9 (median 25.5, range 19-47),	10 (31.2%) F to M, 22 (68.8%) M to F; ratio 1:2.2	-

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Author	Age (years; mean, S.D., range)	Gender	Race
	F to M: 27.8±5.2 (median 27, range 23-37), M to F: 26.4±7.8 (median 24, range 19-47).		
Ruppin	All: 47.0±10.42 (but 2 w/o SRS) (13.8±2.8 yrs post legal name change) (long-term follow-up) F to M: 41.2±5.78, M to F 52.9±10.82	36 (50.7%) F to M, 35 (49.3%) M to F; ratio 1:0.97	-
Smith	Time of surgical request for post-SRS: 30.9 (range 17.7-68.1) Time of follow-up for post-SRS: 35.2 (range 21.3-71.9)	Pre-SRS: 162: 58 (35.8%) F to M, 104 [64.2%] M to F; ratio 1:1.8 Post-SRS: 126: 49 (38.9%) F to M, 77 (61.1%) M to F; ratio 1:1.6	-
Udeze Megeri	M to F: 47.33±13.26 (range 25-80).	40 M to F	-
Wolfradt	Patients & controls: 43 (range 29-67).	30 M to F plus 30 F controls plus 30 M controls.	-

*Data obtained via a survey on a website and distributed at a conference SD=Standard deviation

Panel B (Surgical Series: No Concurrent Controls)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Blanchard et al.	F to M: 32.6, M to F w M partner preference: 33.2, F to M w F partner preference: 47.7 years	Post-GRS: 47 (45.6%) F to M, 56 (54.4%) M to F; ratio 1:1.19. In study: 38 (48.1%) F to M, 32 (40.5%) M to F w M partner preference, 9 (11.4%) M to F w F partner preference; ratio 1:0.8: 0.2	-
Weyers et al.	Post-GRS M to F: 43.1 ±10.4 (long-term follow-up)	50 M to F	-
Wierckx et al.	Time of GRS: 30±8.2 years (range 16 to 49) Time of follow-up: 37.1 ±8.2.4 years (range 22 to 54)	49 M to F	-
Eldh et al.	-	50 (55.6%) F to M, 40 (44.4%) M to F; ratio 1:0.8 There is 1 inconsistency in the text suggesting that these should be reversed.	-
Hess et al.	-	119 M to F	-
Lawrence	Time of GRS: 44±9 (range 18-70)	232 M to F	-
Salvador et al.	Time of follow-up for post-GRS: 36.28±8.94 (range 18-58) (Duration of follow-up: 3.8±1.7 [2-7])	52 M to F	-
Tsoi	Time of initial visit: All: 24.0±4.5, F to M: 25.4±4.4 (14-36), M to F: 22.9±4.6 (14-36). Time of GRS: All: 25.9±4.14, F to M: 27.4±4.0 (20-36), M to F: 24.7±4.3 (20-36).	36 (44.4%) F to M, 45 (55.6%) M to F; ratio 1:1.25	0% 100% Asian

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Gómez-Gil et al. 2012	W & W/O GRS: All: 29.87±9.15 (range 15-61), W/O hormone tx: 25.9±7.5, W current hormone tx: 33.6±9.1. (At hormone initiation: 24.6±8.1).	W/O hormone tx: 38 (56.7%) F to M, 29 (43.3%) M to F; ratio 1:0.8. W hormone tx: 36 (30.0%) F to M, 84 (70.0%) M to F; ratio 1:2.3. Post-GRS: 29 (36.7%) F to M, 50 (63.3%) M to F; ratio 1:1.7.	-
Hepp et al.	W & W/O GRS: 32.2±10.3	W & W/O GRS: 11 (35.5%) F to M; 20 (64.5%) M to F; ratio 1:1.8.	-
Motmans et al.	W & W/O GRS: All (n=140) : 39.9±10.2, F to M: 37.0±8.5, M to F: 42.3±10.4	W & W/O GRS: N=140 63(45.0%) F to M, 77 (55.0%) M to F; ratio 1:1.2 N=103 49 (47.6%) F to M; 54 (52.4%) M to F; ratio 1:1.1	-
Newfield et al.	W & W/O GRS: U.S.+ non-U.S. : 32.8±11.2, U.S. 32.6±10.8	W & W/O GRS: U.S.+ non-U.S.: F to M, 438, U.S.: F to M: 376	89% of 336 respondents Caucasian
Gomez-Gil, et al. 2014	W & W/O Non-genital GRS: 31.2±9.9 (range 16-67).	W & W/O Non-genital GRS: 74 (38.3%) F to M, 119 (61.7%) M to F; ratio 1:1.6.	-
Asscherman	Time of hormone tx: F to M: 26.1±7.6 (16-56), M to F: 31.4±11.4 (16-76)	Met hormone tx requirements: 365 (27.4%) F to M, 966 (72.6%) M to F; ratio 1:2.6. Post-GRS: 343 (29.1%) F to M, 834 (70.9%) M to F; ratio 1:2.4.	-
Johanssen	Time of initial evaluation: F to M: 27.8 (18-46), M to F 37.3 (21-60). Time of GRS: F to M: 31.4 (22-49), M to F 38.2 (22-57). Time of follow-up for post-GRS: F to M: 38.9 (28-53), M to F 46.0 (25-69) (Long-term follow-up)	Approved for GRS: 21 (35%) F to M, 39 (65%) M to F; ratio 1:1.9) Post GRS: 14 (43.8%) F to M; 18 (56.2%) M to F; ratio 1:1.3)	-
Leinung et al.	Time of hormone initiation : F to M: 27.5, M to F 35.5	W & W/O GRS: 50 (20.7%) F to M, 192 M to F (79.3%); ratio 1:3.8. Post-GRS: 32 F to M (35.2%); 59 (64.8%) M to F; ratio 1:1.8.	-

Appendix E

Psychometric and Satisfaction Survey Instruments

Instrument Name and Developer	Development and Validation Information
APGAR Family Adaptability, Partner-ship Growth, Affection, and Resolve <i>Smilkstein</i>	Published in 1978 Initial data: 152 families in the U.S. A "friends" component was added in 1983. Utility has challenged by many including Gardner 2001
Beck Depression Inventory <i>Beck, Ward, Mendelson, Mock, & Erbaugh</i>	Published initially in 1961 with subsequent revisions It was initially evaluated in psychiatric patients in the U.S.A.

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	Salkind (1969) evaluated its use in 80 general outpatients in the UK. It is copyrighted and requires a fee for use
Bem Sex Role Inventory <i>Bem</i>	Published 1974 Initial data: 100 Stanford Undergraduates 1973 update: male 444; female 279 1978 update: 470; female 340
Body Image Questionnaire <i>Clement & Lowe</i>	Validity study published 1996 (German) Population: 405 psychosomatic patients, 141 medical students, 208 sports students
Body Image Scale <i>Lindgren & Pauly</i> <i>(Kuiper, Dutch adaptation 1991)</i>	1975 Initial data: 16 male and 16 female transsexual patients in Oregon
Crown Crisp Experiential Index (formerly Middlesex Hospital Questionnaire) <i>Crown & Crisp</i>	Developed circa 1966 Manual published 1970 Initial data: 52 nursing students while in class in the UK
(2nd) European Quality of Life Survey <i>Anderson, Mikulić, Vermeylen, Lyly-Yrjanainen, & Zigante,</i>	Published in 2007 The pilot survey was tested in the UK and Holland with 200 interviews. The survey was revised especially for non-response questions. Another version was tested in 25 persons of each of the 31 countries to be surveyed. Sampling methods were devised. 35,634 Europeans were ultimately surveyed. Additional updates
Female Sexual Function Index <i>Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, Ferguson, D'Agostino Wiegel, Meston, & Rosen</i>	Published in 2000 Initial data: 131 normal controls & 128 age-matched subjects with female sexual arousal disorder from 5 U.S. research centers. Updated 2005: the addition of those with hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia/vaginismus, & multiple sexual dysfunctions (n=568), plus more controls (n=261).
Fragebogen zur Beurteilung des eigenen Körpers <i>Strauss</i>	Published 1996 (German)
Freiberg Personality Inventory <i>Fahrenberg, Hampel, & Selg</i>	7 th edition published 2001, 8 th edition in 2009 (Not in PubMed) German equivalent of MMPI
"gender identity disorder in childhood" <i>Smith, van Goozen, Kuiper, & Cohen-Kettenis</i>	11 items derived from the Biographical Questionnaire for Trans-sexuals (Verschoor Poortinga 1988) (Modified by authors of the Smith study)
Gender Identity Trait Scale <i>Altstotter-Gleich</i>	Published 1989 (German)
General Health Questionnaire <i>Goldberg & Blackwell (initial study)</i> <i>Goldberg & Williams (manual)</i>	Initial publication 1970 Manual published ?1978, 1988 (Not in PubMed) Initial data: 553 consecutive adult patients in a single UK primary care practice were assessed. Sample of 200 underwent standardized psychiatric interview. Developed to screen for hidden psychological morbidity. Proprietary test. Now 4 versions.
Hospital Anxiety & Depression Scale <i>Zigmond & Snaith</i>	Published in 1983 Initial data: Patients between 16 & 65 in outpatient clinics in the UK

Instrument Name and Developer Case 7:16-cv-00108-O	Development and Validation Information Document Filed 10/21/16 Page 818 of 919
	>100 patients; 2 refusals. 1 st 50 compared to 2 nd 50.
Inventory of Interpersonal Problems <i>Horowitz</i>	Published 1988 Initial data: 103 patients about to undergo psychotherapy; some patients post psychotherapy (Kaiser Permanente-San Francisco) Proprietary test
King's Health Questionnaire <i>Kelleher, Cardozo, Khullar, & Salvatore</i>	1997 Initial data: 293 consecutive women referred for urinary incontinence evaluation in London Comparison to SF-36
Minnesota Multi-phasic Personality Inventory <i>Hathaway & McKinley</i> <i>Butcher, Dahlstrom, Graham, & Tellegen</i>	Published in 1941 Updated in 1989 with new, larger, more diverse sample. MMPI-2: 1,138 men & 462 women from diverse communities & several geographic regions in the U.S.A. The test is copyrighted.
Modified Androphilia-Gynephilia Index	Neither the underlying version or the Blanchard modified version could be located in PubMed (Designed by the author of the Blanchard et al. study)
"post-operative functioning 13 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
"post-operative functioning 21 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
Scale for Depersonalization Experiences <i>Wolfradt</i>	Unpublished manuscript 1998 (University of Halle) (Designed by 1 of the authors of the Wolfradt study)
"sex trait function" <i>Cohen-Kettenis & van Goozen</i>	Published 1997 Assessed in 22 adolescents (Designed by 1 of the authors of the Smith Study)
Self-Esteem Scale <i>Rosenberg</i>	Published 1965 (Not in PubMed) Initial data: 5,024 high-school juniors & seniors from 10 randomly selected New York schools
Short-Form 36 <i>RAND</i> <i>Ware & Sherbourne 1992</i> <i>McHorney, Ware, & Raczek 1993</i>	Originally derived from the Rand Medical Outcomes Study (n=2471 in version 1; 6742 in version 2 1989). The earliest test version is free. Alternative scoring has been developed. There is a commercial version with a manual.
Social Anxiety & Distress Scale <i>Watson & Friend</i>	Initial publication in 1969 Requires permission for use
Social Support Scale <i>Van Tilburg 1988</i>	Published 1988 (Dutch) (Not in PubMed)
Spielberger State & Trait Anxiety Questionnaire <i>Spielberger, Gorsuch, Lushene, Vagg, & Jacobs</i>	Current format published in 1983 Proprietary test
Symptom Checklist-90 <i>Derogatis, Lipman, Covi</i>	Published in 1973 & 1977

<i>Derogatis & Cleary</i>	Reportedly with normative data for psychiatric patients (in- & out-patient) & normal subjects in the U.S. Has undergone a revision Requires qualification for use
Tennessee Self-Concept Scale <i>Fitts & Warren</i>	In use prior to 1988 publication. Initial data: 131 psychiatric day care patients. Updated manual published 1996. Update population >3000 with age stratification. No other innformation available. Requires qualification for use
Utrecht Gender Dysphoria Scale <i>Cohen-Kettenis & van Goozen</i>	Published in 1997 Initial population: 22 transgender adolescents who underwent reassignment surgery. (Designed by 1 of the authors of the Smith study)
WHO-Quality of Life (abbreviated version) <i>Harper for WHO group</i>	Field trial version released 1996 Tested in multiple countries. The Seattle site consisted of 192 of the 8294 subjects tested). Population not otherwise described. The minimal clinically important difference has not been determined. Permission required

Althof et al., 1983; Greenberg, Frank, 1965; Gurtman, 1996; Lang, Vernon, 1977; Paap et al., 2012; Salkind et al., 1969; Vacchiano, Strauss, 1968.

Appendix F

Endpoint Data Types and Sources

Panel A (Controlled Studies)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substan- tive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne 2011	Yes	-	-	-	-	Mortality (Suicide, Cardiovascular Disease [possible adverse events from Hormone Tx], Cancer), Psych hx & hospitalization, Suicide attempts

Author	National Data	Instrument w/ Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne Landén	Yes	-	-	-	Includes demographics*	Education, Employment, Formal application for reversal of status, Psych dx & tx, Substance abuse** More elements in earlier paper
Beatrice	-	MMPI form R, TSCS	-	-	Demographic	Education, Income, Relationships
Haraldsen	-	SCL-90/90R	-	-	Demographic	DSM Axis 1, II, V (GAF), Substance abuse
Heylens	-	SCL-90	-	Yes-2	Demographic	Employment, Relationships, Substance abuse, Suicide attempts
Ainsworth	-	Likely SF-36v2*	-	Yes-1	Demographic	-
Ruppin	-	SCL-90R	BSRI, FPI-R, IIP	Yes-2	Demographic	Adverse events from surgery, Employment, Psych tx, Relationships, Substance abuse
Smith	-	MMPI-short, SCL-90?R	BIS, UGDS, ? Cohen-Kettenis', Doorn's x2, (Gid-c, SSS)	Yes-1 or 2	Demographic	Adverse events from surgery, Employment, Relationships
Udeze Megeri	-	SCL-90R	BDI, GHQ, HADS, STAI-X1, STAI-X2	-	-	Psych eval & ICD-10 dx
Kuhn	-	-	KHQ	Yes-1	Demographic	Relationships
Mate-Kole 1990	-	-	BSRI, CCEI	Yes-1	Demographic	Employment (relative change), Psych hx, Suicide hx
Wolfradt	-	-	BIQ, GITS, SDE, SES	Yes-1	-	-
Kraemer	-	-	FBeK	-	Demographic	-
Mate-Kole 1988	-	-	BSRI, CCEI	-	Demographic	Employment, Psych hx, Suicide hx,
Kockott	-	-	-	Yes-1	Demographic	

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
						Employment, Income, Relationships, Suicide attempts
Meyer	-	-	-	Yes-1	Demographic	Education, Employment, Income, Psych tx, Phallus removal request
Rakic	-	-	-	Yes-1	Demographic	Employment, Relationships

Panel B (Surgical Series: No Concurrent Controls)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Weyers	-	SF-36	FSFI	Yes-2	Demographic	Hormone levels, Adverse events from surgery, Relationships
Blanchard	-	SCL-90R	(AG)	Yes-1	Demographic	Education, Employment, Income, Relationships, Suicide (Incidental finding)
Wierckx	-	SF-36	-	Yes-3	Demographic	Hormone levels, Adverse events from surgery, Relationships
Eldh	-	-	-	Yes-1	-	Adverse events from surgery, Employment, Relationships, Suicide attempts
Hess	-	-	-	Yes-1	-	-
Lawrence	-	-	-	Yes-4	Demographic	Adverse events from surgery

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Salvador	-	-	-	Yes-1	Demographic	Relationships
Tsoi	-	-	-	Yes-1	Demographic	Education, Employment, Relationships (relative change)

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Asscheman et al.	Yes	-	-	-	Demographic	Mortality (HIV, Possible adverse events from Hormone Tx, Substance abuse, Suicide)
Motmans et al.	-	SF36 EQOLS (2 nd)	-	-	Demographic	Education, Employment, Income, Relationships
Newfield et al.	-	SF-36v2	-	-	Demographic	Income
Gómez-Gil et al. 2014	-	WHOQOL-BREF	APGAR	Yes-1	Demographic	Education, Employment, Relationships
Gómez-Gil et al. 2012	-	-	HADS, SADS	-	Demographic	Education, Employment, Living arrangements
Hepp et al.	-	-	HADS	-	Demographic	DSM Axis I& II Psych dx
Johansson et al.	-	-	-	Yes-1	Demographic	Axis V change (Pt & Clinician) Employment (relative change) Relationship (relative change)
Leinung et al.	-	-	-	-	Demographic	Employment, Disability, DVT, HIV status, Psych dx

Author	National Data	Instrument w/ Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
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*Listed as San Francisco-36 in manuscript

** From medical charts & verdicts ?=Possibly self-designed

AG=Androphilia-Gynephilia Index (investigator designed 1985) (used more for classification)

APGAR=Family Adaptability, Partnership growth, Affection, and Resolve

BDI=Beck Depression Inventory

BIQ=Body Image Questionnaire

BIS=Body Image Scale

BSRI=Bem Sex Role Inventory

CCEI=Crown Crisp Experiential Index

Cohen-Kettenis'= Sex trait function (An author helped design)

Dorn's x2= Post-operative functioning 13 items (An author helped design)

Post-operative functioning 21 items (An author helped design)

EQOLS (2nd)=2nd European Quality of Life Survey

FBeK=Fragebogen zur Beurteilung des eigenen Korpers

FPI-R=A version of the Freiberg Personality Inventory

FSFI+Female Sexual Function Index

GHQ=General Health Questionnaire

Gid-c=Gender identity disorder in childhood (used more for predictors) (An author helped design)

GITS=Gender Identity Trait Scale

HADS=Hospital Anxiety Depression Scale

IIP=Inventory of Interpersonal Problems

KHQ=King's Health Questionnaire

MMPI=Minnesota Multi-phasic Personality Inventory

SADS=Social Anxiety & Distress Scale

SCL-90 (±R)=A version of the Symptom Checklist 90

SDE=Scale for Depersonalized Experiences (An author designed)

SES=Self-Esteem Scale

SF-36 (v2)=Short Form-36(version2)

SSS=Social Support Scale (used more for predictors)

STAI-X1, STAI-X2=Spielberger State and Trait Anxiety Questionnaire

TSCS=Tennessee Self-Concept Scale

UGDS=Utrecht Gender Dysphoria Scale (An author helped design)

WHOQOL-BREF=World Health Organization-Quality of Life (abbreviated version)

Appendix G.

Longitudinal Studies Which Used Patients as Their Own Controls and Which Used Psychometric Tests with Extensive Normative Data or Longitudinal Studies Which Used National Data Sets

Author	Test	Patient and Data Loss	Results
Psychometric Test			
Heylens et al. Belgium 2014	SCL-90R	90 applicants for SRS were recruited. •8 (8.9%) declined participation. •12 (13.3%) excluded b/c GID-NOS dx.	At t=0, the mean global "psychoneuroticism" SCL-90R score, along with scores of 7 of 8 subscales, were statistically more pathologic than the general population.

Author	Test	Patient and Data Loss	Results
		<p>•12 (13.3%) did not complete the treatment sequence b/c of psychiatric/physical co-morbidity, personal decision for no tx, or personal decision for only hormone tx.</p> <p>•1 (1.1%) committed suicide during follow-up.</p> <p>57 (63.3% of recruited) entered the study.</p> <p>•1 (12.2% of initial recruits) had not yet received SRS by study close.</p> <p>46 (51.1% of recruited) underwent serial evaluation</p> <p>•The test was not completed by 1 at t=0, 10 at t=1 (after hormone tx), & 4 at t=2 (after SRS)</p> <p>missing data for another 1.1% to 11.1%.</p>	<p>After hormone tx, the mean score for global "psychoneuroticism" normalized & remained normal after reassignment surgery.</p>
Ruppin,Pfafflin, Germany 2015	SCL-90R	<p>The number in the available patient pool was not specified.</p> <p>140 received recruitment letters.</p> <p>•2 (1.4% of those with recruitment letters) had died.</p> <p>•1 (0.7%) was institutionalized.</p> <p>•5 (3.6%) were ill.</p> <p>•8 (5.7%) did not have time.</p> <p>•8 (5.7%) stated that GD was no longer an issue.</p> <p>•8 (5.7%) provided no reason.</p> <p>•28 (20.0%) declined further contact.</p> <p>•9 (6.4%) were lost to follow-up.</p> <p>71 (50.7%) agreed to participate.</p> <p>•2 (1.4%) had not undergone SRS</p> <p>•The test was not completed by 9.</p> <p>missing data for another 6.4%.</p>	<p>At t=0, the "global severity index "SCL-90R score was 0.53 ± 0.49. At post-SRS follow-up the score had decreased to 0.28 ± 0.36.</p> <p>The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 0-4.</p> <p>In the same way, all of the subscale scores were statistically different, but the effect size was reported as large only for "interpersonal sensitivity": 0.70 ± 0.67 at t=0 and 0.26 ± 0.34 post-SRS.</p>
Smith et al. Holland 2005	MMPI SCL-90	<p>The number in the available adult patient pool was not specified.</p> <p>325 adult & adolescent applicants for SRS were recruited.</p> <p>•103 (31.7%) were not eligible to start hormone tx & real-life experience.</p>	<p>Most of the MMPI scales were already in the normal range at the time of initial testing.</p>

Author	Test	Patient and Data Loss	Results
		<ul style="list-style-type: none"> • 34 (10.7%) discontinued hormone tx 162 (an unknown percentage of the initial recruitment) provided pre-SRS test data. • 36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete post-SRS testing. 	<p>At t=0, the global "psychoneuroticism" SCL-90 score, which included the drop-outs, was 143.0 ± 40.7.</p> <p>At post SRS-follow-up, the score had decreased to 120.3 ± 31.4.</p> <p>The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 90 to 450, with higher scores consistent with more psychological instability.</p>
Udeze, et al. 2008 Megeri, Khoosal 2007 UK	SCL-90R	<p>The number in the available patient pool was not specified. 40 subjects were prospectively selected.</p> <ul style="list-style-type: none"> • Post-operative testing was conducted within 6 months to minimize previously determined loss rates. 	<p>At t=0, the mean raw global score was 48.33. At post-SRS follow-up, the mean score was 49.15.</p> <p>There were no statistically significant changes in the global score or for any of the subscales.</p>
National Databases			
Dehjne Sweden 2011	Swedish National Records	<p>804 with GID in Sweden 1973 to 2003 were identified.</p> <ul style="list-style-type: none"> • 480 (59.7%) did not apply or were not approved for SRS 324 (40.3%) underwent SRS. • All were followed. <p>3240 controls of the natal sex and 3240 controls of the reassigned gender were randomly selected from national records</p>	<p>All cause mortality was higher ($n=27[8\%]$) than in controls (H.R. 2.8 [1.8-4.3]) even after adjustment for covariants. Divergence in survival curves was observed after 10 years. The major contributor was completed suicide ($n=10 [3\%]$; adjusted H.R. 19.1 [5.8-62.9]).</p> <p>Suicide attempts were more common ($n=29 [9\%]$) than in controls (adjusted H.R. 4.9 [2.9-8.5]).</p>

Author	Test	Patient and Data Loss	Results
			Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common n= 64 [20%] than in controls (H.R. 2.8 [2.0–3.9]) even after adjusting for prior psychiatric morbidity.
Dhejne et al. 2014 Landén et al. 1998 Sweden	Swedish National Registry	767 applied for SRS/legal status (1960-2010) •25 (3.3%) applications denied. •61 (8.0%) not granted full legal status 681 (88.7%) underwent SRS. •All were followed.	15 formal applications for reversal to natal/original gender (2.2% of the SRS population) were identified thus far (preliminary number). (Does not reflect other manifestations of regret such as suicide.)

GID=NOS=Gender Identity Disorder-Not Otherwise Specified HR=Hazard Ratio SRS=Sex reassignment surgery
Tx=Treatment [Back to Top](#)

Bibliography

ACA 2010: Patient Protection and Affordable Care Act, Pub. L. No. 111 -148, §3502, 124 Stat. 119, 124 (2010).

Ahmed SF, Morrison S, Hughes IA. Intersex and gender assignment; the third way? *Arch Dis Child*. 2004 Sep;89(9):847-50. PMID:> 15321864.

Ainsworth T, Spiegel J. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. *Qual Life Res*. 2010 Sep;19(7):1019-24. Epub 2010 May 12. PMID: 20461468.

Altstotter-Gleich, C. (1989). *Theoriegeleitete Itemkonstruktion und -auswahl: Eine Modifikation des Einsatzes der Repertory-Grid-Technik dargestellt am Beispiel der Erfassung der Geschlechtsidentität* [Theory oriented item construction and selection: A modification of the use of the Repertory-Grid- Technique as shown at the exemple of the assessment of gender identity], Verlag fur empirische Padagogik, Landau. German. (Not in PubMed)

Althof SE, Lothstein LM, Jones P, Shen J. An MMPI subscale (Gd): to identify males with gender identity conflicts. *J Pers Assess*. 1983 Feb;47(1):42-9. PMID: 6834232.

American Medical Association House of Delegates resolution 122 (A-08) proposal *Removing Financial Barriers to Care for Transgender Patients*. 2008.

American Psychological Association (APA). Guidelines for Psychological Practice with Transgender and Gender Nonconforming People. *American Psychologist*: 2015: Adopted by the Council of Representatives, August 5 & 7, 2015. www.apa.org/practice/guidelines/transgender.pdf (publication pending).

Antoszewski B, Bratoś R, Sitek A, Fijałkowska M. Long-term results of breast reduction in female-to- male transsexuals. *Pol Przegl Chir.* 2012 Mar;84(3):144-51. PMID: 22659357.

Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-Aranda F. Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur Psychiatry*. 2015 Sep;30(6):807-15. Epub 2015 May 26. PMID: 26021270.

Asscheman H, Gooren LJ; Eklund PL. Mortality and morbidity in transsexual patients with cross- gender hormone treatment. *Metabolism*. 1989 Sep;38(9):869-73. PMID: 2528051.

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011 Apr;164(4):635-42. Epub 2011 Jan 25. PMID: 21266549.

Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola M, Mueller A, Kuhn A, Dhejne C, Morel- Journel N, Gooren L. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia*. 2014 Sep;46(7):791-5. Epub 2013 Aug 15. PMID: 23944849.

Auer M, Fuss J, Stalla G, Athanasoulia A. Twenty years of endocrinologic treatment in transsexualism: analyzing the role of chromosomal analysis and hormonal profiling in the diagnostic work-up. *Fertil Steril* 2013 Oct;100(4):1103-10. Epub 2013 Jun 27. PMID: 23811520

Auerbach JD. The iPrEx results: lifting hopes, raising questions. *BETA*. 2010 Summer-Fall;22 (4):47-9. PMID: 21591604.

Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T. Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *J Sex Med*. 2011 Jun;8(6):1686-93. Epub 2011 Apr 7. PMID: 21477021.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011 Apr;64(4):401-6. Epub 2011 Jan 5. PMID: 21208779.

Bandini E, Fisher AD, Ricca V, Ristori J, Meriggiola MC, Jannini EA, Manieri C, Corona G, Monami M, Fanni E, Galleni A, Forti G, Mannucci E, Maggi M. Childhood maltreatment in subjects with male-to-female gender identity disorder. *Int J Impot Res*. 2011 Nov-Dec;23(6):276-85. Epub 2011 Aug 11. PMID: 21833007.

Bao AM, Swaab DF. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. *Front Neuroendocrinol*. 2011 Apr;32(2):214-26. Epub 2011 Feb 18. PMID: 21334362.

Baral S, Poteat T, Strömdahl S, Wirtz A, Guadamuz T, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013 Mar;13(3):214- 22. Epub 2012 Dec 21. PMID: 23260128.

Barrett J. (1998) *Psychological and social function before and after phalloplasty*. University of London. Institute of Psychiatry. Thesis (MSc). King's College London. Catalogue #000457428 or IJT. 1998; 2:1 or <http://gendertrust.org.uk/wp-content/uploads/2013/02/13-Psychological-and-Social-Function-Before-and-After-Phal..pdf>.

Barrington C, Wejnert C, Guardado ME, Nieto AI, Bailey GP. Social network characteristics and HIV vulnerability among transgender persons in San Salvador: identifying opportunities for HIV prevention strategies. *AIDS Behav*. 2012 Jan;16(1):214-24. PMID: 464738.

Bartlett NH, Vasey PL. A retrospective study of childhood gender-atypical behavior in Samoan fa'afafine. *Arch Sex Behav*. 2006 Dec;35(6):659-66. Epub 2006 Aug 15. PMID: 16909317.

Bartolucci C, Gómez-Gil E, Salamero M, Esteva I, Guillamón A, Zubiaurre L, Molero F, Montejo A. Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. *J Sex Med* .2015 Jan;12(1):180-8. Epub 2014 Nov 17. PMID: 25401972.

Baumeister S, Sohn M, Domke C, Exner K. [Phalloplasty in female-to-male transsexuals: experience from 259 cases]. *Handchir Mikrochir Plast Chir*. 2011 Aug;43(4):215-21. Epub 2011 Aug 11. PMID: 21837614.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. *J Nerv Ment Dis*. 1985 Jun;173(6):358-65. PMID: 3998721.

Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* .1961 Jun;4:561-71. PMID: 13688369.

Bentz EK, Hefler LA, Kaufmann U, Huber JC, Kolbus A, Tempfer CB. A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to- female transsexualism. *Fertil Steril*. 2008 Jul;90(1):56-9. Epub 2007 Sep 4. PMID: 17765230.

Bentz EK, Pils D, Bilban M, Kaufmann U, Hefler LA, Reinthaller A, Singer CF, Huber JC, Horvat R, Tempfer CB. Gene expression signatures of breast tissue before and after cross-sex hormone therapy in female-to-male transsexuals. *Fertil Steril*. 2010 Dec;94(7):2688-96. Epub 2010 May 26. PMID: 20537635.

Bem, S. L. (1974). The measurement of psychological androgyny. *Journal of Consulting and Clinical Psychology*. 1974; 42:155-162. (Not in PubMed)

Berry MG, Curtis R, Davies D. Female-to-male transgender chest reconstruction: a large consecutive, single-surgeon experience. *J Plast Reconstr Aesthet Surg*. 2012 Jun;65(6):711-9. Epub 2011 Dec 19. PMID: 22189204.

Besnier, N. (1994). Polynesian gender liminality through time and space. In G.Herdt (Ed.), *Third> sex, third gender: Beyond sexual dimorphism in culture and history*. New York: Zone Books.

Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol*. 1988 Sep;61 (Pt 3):255-66. PMID: 3179248.

Bith-Melander P, Sheoran B, Sheth L, Bermudez C, Drone J, Wood W, Schroeder K. Understanding sociocultural and psychological factors affecting transgender people of color in San Francisco. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):207-20. PMID: 20416495.

Bjerrome Ahlin H, Kölby L, Elander A, Selvaggi G. Improved results after implementation of the Ghent algorithm for subcutaneous mastectomy in female-to-male transsexuals. *J Plast Surg Hand Surg*. 2014 Dec;48(6):362-7. Epub 2014 Mar 11. PMID: 24611803.

A-Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304. PMID: 4008715.

B-Blanchard R. Typology of male-to-female transsexualism. *Arch Sex Behav*. 1985 Jun;14(3):247-61. PMID: 4004548.

C-Blanchard RJ, Blanchard DC, Flannelly KJ. Social desirability response set and systematic distortion in the self-report of adult male gender patients. *Behav Processes*. 1985 Aug;11(2):209-13. doi: 10.1016/0376-6357(85)90062-2. PMID: 24895927.

D-Blanchard, R. (1985). *Research methods for the typological study of gender disorders in males*. In B. W. Steiner (Ed.), *Gender dysphoria: Development, research, management* (pp. 227-257). New York: Plenum Press.

Blanchard R, Clemmensen LH, Steiner BW. Heterosexual and homosexual gender dysphoria. *Arch Sex Behav*. 1987 Apr;16(2):139-52. PMID: 3592961.

Blanchard R, Steiner BW, Clemmensen LH, Dickey R. Prediction of regrets in postoperative transsexuals. *Can J Psychiatry*. 1989 Feb;34(1):43-5. PMID: 2924248.

Bockting W, Coleman E, De Cuypere G. Care of transsexual persons. *N Engl J Med*. 2011 Jun 30;364 (26):2559-60; author reply 2560. PMID: 21714669.

Bodlund O, Armelius K. Self-image and personality traits in gender identity disorders: an empirical study. *J Sex Marital Ther*. 1994 Winter;20(4):303-17. PMID: 7897678.

Bodlund O, Kullgren G. Transsexualism general outcome and prognostic factors: a five-year follow- up study of nineteen transsexuals in the process of changing sex. *Arch Sex Behav*. 1996 Jun;25 (3):303-16. PMID: 8726553.

Boehmer AL, Brinkmann AO, Sandkuijl LA, Halley DJ, Niermeijer MF, Andersson S, de Jong FH, Kayserili H, de Vroede MA, Otten BJ, Rouwé CW, Mendonça BB, Rodrigues C, Bode HH, de Ruiter PE, Delemarre-van de Waal HA, Drop SL. 17Beta-hydroxysteroid dehydrogenase-3 deficiency: diagnosis, phenotypic variability, population genetics, and worldwide distribution of ancient and de novo mutations. *J Clin Endocrinol Metab*. 1999 Dec;84(12):4713-21. PMID: 10599740.

Bonifacio HJ, Rosenthal SM. Gender Variance and Dysphoria in Children and Adolescents. *Pediatr Clin North Am*. 2015 Aug;62(4):1001-16. Epub 2015 Jun 11. PMID: 26210629.

Borsboom D, Mellenbergh GJ, van Heerden J. The theoretical status of latent variables. *Psychol Rev*. 2003 Apr;110(2):203-19. PMID: 12747522.

Bouman M, van Zeijl M, Buncamper M, Meijerink W, van Bodegraven A, Mullender M. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. *J Sex Med*. 2014 Jul;11(7):1835-47. Epub 2014 Apr 4. PMID: 24697986.

Bowman E, Oprea G, Okoli J, Gundry K, Rizzo M, Gabram-Mendola S, Manne U, Smith G, Pambuccian S, Bumpers HL. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. *Breast J*. 2012 May-Jun;18(3):242-7. PMID: 22583194.

Broderick JP. Devices and clinical trials: overview and equipoise. *Stroke*. 2013 Jun;44(6 Suppl 1):S3-6. PMID: 23709721.

Brown L (Ed.). (1997) *Two Spirit People: American Indian, lesbian women and gay men*. Routledge.

Bye L, Gruskin E, Greenwood, G, Albright V, Krotki K. California Lesbians, Gays, Bisexuals, and Transgender (LGBT) Tobacco Use Survey – 2004. *Sacramento, CA: California Department of Health Services*, 2005. (Not in PubMed)

Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R, Pleak RR, Tompkins DA. American Psychiatric Association. Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav* 2012 Aug;41(4):759-96. PMID: 22854940.

Callens N, De Cuypere G, Van Hoecke E, T'sjoen G, Monstrey S, Cools M, Hoebeke P. Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis: a review. *J Sex Med*. 2013 Dec;10(12):2890-903. Epub 2013 Aug 23. PMID: 23981815.

Callens N, Hoebeke P. Phalloplasty: A panacea for 46, XY disorder of sex development conditions with penile deficiency? *Endocr Dev*. 2014;27:222-33. Epub 2014 Sep 9. PMID: 25247659.

Cameron D. Language, gender, and sexuality: Current issues and new directions. *Applied Linguistics*. 2005; 26(4):482-502. (Not in PubMed)

Casella R, Bubendorf L, Schaefer D, Bachmann A, Gasser T, Sulser T. Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int*. 2005;75(3):288-90. PMID: 16215322.

Cantor JM. New MRI studies support the Blanchard typology of male-to-female transsexualism. *Arch Sex Behav*. 2011 Oct;40(5):863-4. PMID: 21739338.

Cebula H, Pham TQ, Boyer P, Froelich S. Regression of meningiomas after discontinuation of cyproterone acetate in a transsexual patient. *Acta Neurochir (Wien)*. 2010 Nov;152(11):1955-6. Epub 2010 Sep 3. PMID: 20811919.

Cerwenka S, Nieder T, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Kreukels B, Richter-Appelt H. Sexual behavior of gender-dysphoric individuals before gender-confirming interventions: a European multicenter study. *J Sex Marital Ther* 2014;40(5):457-71. PMID: 24846436.

Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet*. 2005 Mar 26-Apr 1;365(9465):1159-62. PMID: 15794971.

Chen S, McFarland W, Thompson HM, Raymond HF. Transmen in San Francisco: what do we know from HIV test site data? *AIDS Behav*. 2011 Apr;15(3):659-62. PMID: 21153048.

Chinas, B. (1995). Isthmus Zapotec attitudes toward sex and gender anomalies. In S. O. Murray (Ed.), *Latin American male homosexualities* (pp. 293-302). Albuquerque, NM: University of New Mexico Press.

Chiong W. The real problem with equipoise. *Am J Bioeth.* 2006 Jul-Aug;6(4):37-47. PMID: 16885104.

CHIS 2009: California Health Interview Survey, 2009. "AskCHIS" via the UCLA Center for Health Policy Research date website ask.chis.ucla.edu/.

Chong JM. Social assessment of transsexuals who apply for sex reassignment therapy. *Soc Work Health Care.* 1990;14(3):87-105. PMID: 2367927.

Claes L, Bouman W, Witcomb G, Thurston M, Fernandez-Aranda F, Arcelus J. Non-suicidal self- injury in trans people: associations with psychological symptoms, victimization, interpersonal functioning, and perceived social support. *J Sex Med.* 2015 Jan;12(1):168-79. Epub 2014 Oct 6. PMID: 25283073.

Clement U, Löwe B. [Validation of the FKB-20 as scale for the detection of body image distortions in psychosomatic patients]. *Psychother Psychosom Med Psychol.* 1996 Jul;46(7):254-9. German. PMID: 8765897.

Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *J Homosex.* 2006;51(3):53-69. PMID: 17135115.

CMS Office of Minority Health. New Directions in CMS Disparities Research: Sexual Orientation & Gender Identity. 2015. Academy Health Annual Research Meeting, Minneapolis, Minnesota.

CMS Office of Minority Health. If You Build It, They Will Come: Accessing and Utilizing HHS LGBTI Data and Information Products. 2015. Gay and Lesbian Medical Association Meeting, Portland, Oregon.

Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997 Feb;36(2):263-71. PMID: 9031580.

A Cohen-Kettenis P. Psychological long-term outcome in intersex conditions. *Horm Res*. 2005;64 Suppl 2:27-30. PMID: 16286767.

B Cohen-Kettenis PT. Gender change in 46 XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005 Aug;34(4):399-410. PMID: 16010463.

Cohen-Kettenis P, Pfäfflin F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Arch Sex Behav*. 2010 Apr;39(2):499-513. PMID: 19838784.

Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress

in gender identity disorder, independently of the attachment style. *J Sex Med*. 2013 Dec;10(12):3049-58. Epub 2013 Apr 9. PMID: 23574768.

Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology*. 2014 Jan;39:65-73. Epub 2013 Oct 10. PMID: 24275005.

Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, Quagliarella L, Brescia F, Natilla LC, Loverro G, Todarello O. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *J Psychosom Res*. 2015 Apr;78(4):399-406. Epub 2015 Feb 10. PMID: 25691225.

Coleman E, Colgan P, Gooren L. Male cross-gender behavior in Myanmar (Burma): A description of the acault. *Arch Sex Behav*. 1992 Jun;21(3):313-21. PMID: 1535191.

Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Oosterleyckx P, O'Neill G, Oudenhout AA, Eurlings J, Lethinckx E, Lofgren DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R, Wylie KR, Zucker K. World Professional Association for Transgender Health (formerly the Harry Benjamin International Gender Dysphoria Association). Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People (Version 7). *Int J Transgend*. 2011;13:165–232. © 2012 World Professional Association for Transgender Health (WPATH). (not in Pubmed) www.wpath.org/uploaded_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf.

Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from

a household probability sample of adults. *Am J Public Health*. 2012 Jan;102(1):118-22. Epub 2011 Nov 28. PMID: 22095354.

Corsello SM, Di Donna V, Senes P, Luotto V, Ricciato MP, Paragliola RM, Pontecorvi A. Biological aspects of gender disorders. *Minerva Endocrinol*. 2011 Dec;36(4):325-39. PMID: 22322655.

Costa L M, Matzner A. (2007). *Male bodies, women's souls: Personal narrative of Thailand's transgendered youth*. Routledge.

Costantino A, Cerpolini S, Alvisi S, Morselli P, Venturoli S, Meriggiola M. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther*. 2013;39(4):321-35. Epub 2013 Mar 7. PMID: 23470169.

Cregten-Escobar P, Bouman M, Buncamper M, Mullender M. Subcutaneous mastectomy in female-to-male transsexuals: a retrospective cohort-analysis of 202 patients. *J Sex Med* 2012 Dec;9(12):3148- 53. PMID: 23470169.

Crown S, Crisp AH. A short clinical diagnostic self-rating scale for psychoneurotic patients. The Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry*. 1966 Sep;112(490):917-23. PMID: 5970912.

Crown S, Duncan KP, Howell RW. Further evaluation of the Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry*. 1970 Jan;116(530):33-7. PMID: 5411005.

Crown S. The Middlesex Hospital Questionnaire (MHQ) in clinical research. A review. *Mod Probl Pharmacopsychiatry*. 1974;7(0):111-24. PMID: 4607280.

Cupisti S, Giltay EJ, Gooren LJ, Kronawitter D, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril*. 2010 Dec;94 (7):2647-53. Epub 2010 May 7. PMID: 20451188.

Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. [February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf](http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf).

De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Vansteenwegen A, Rubens R. Sexual and physical health after sex reassignment surgery. *Arch Sex Behav*. 2005 Dec;34(6):679-90. PMID: 16362252.

De Cuypere G, Elaut E, Heylens G, van Maele G, Selvaggi G, T'Sjoen G, Rubens R, Hoebeke R, Monstrey S. Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. *J Sexol*. 2006;15:126-33. (Not in PubMed)

De Cuypere G, Van Hemelrijck M, Michel A, Carael B, Heylens G, Rubens R, Hoebeke P, Monstrey S. Prevalence and demography of transsexualism in Belgium. *Eur Psychiatry*. 2007 Apr;22(3):137- 41. Epub 2006 Dec 26. PMID: 17188846.

Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovich C, Song F, Petticrew M, Altman DG; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess*. 2003;7(27):iii-x, 1-173. PMID: 14499048.

Deipolyi AR, Han SJ, Parsa AT. Development of a symptomatic intracranial meningioma in a male- to-female transsexual after initiation of hormone therapy. *J Clin Neurosci*. 2010 Oct;17(10):1324-6. Epub 2010 Jul 1. PMID: 20594855.

A-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci.* 1974 Jan;19(1):1-15. PMID:

B-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL). A measure of primary symptom dimensions. *Mod Probl Pharmacopsychiatry.* 1974;7(0):79- 110. PMID: 4607278.

Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. *Br J Soc Clin Psychol.* 1977 Nov;16(4):347-56 PMID: 588890.

Derogatis LR, Meyer JK, Vazquez N. A psychological profile of the transsexual. I. The male. *J Nerv Ment Dis.* 1978 Apr;166(4):234-54. PMID: 650186.

Deutsch M, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. *Obstet Gynecol.* 2015 Mar;125(3):605-10. PMID: 25730222.

de Vries A, Kreukels B, Steensma T, Doreleijers T, Cohen-Kettenis P. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res* 2011 Apr 30;186 (2-3):414-8. PMID: 20801524.

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011;6 (2):e16885. Epub 2011 Feb 22. PMID: 21364939.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Arch Sex Behav.* 2014 Nov;43(8):1535-45. Epub 2014 May 29. PMID: 24872188.

Dhillon R, Bastiampillai T, Krishnan S, Opray N, Tibrewal P. Transgender late onset psychosis: the role of sex hormones. *Aust N Z J Psychiatry*. 2011 Jul;45(7):603. Epub 2011 May 5. PMID: 21542781.

Diamond M. Developmental, sexual and reproductive neuroendocrinology: historical, clinical and ethical considerations. *Front Neuroendocrinol*. 2011 Apr;32(2):255-63. Epub 2011 Feb 18. PMID: 21310174.

Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann M, Mueller A. Endocrine treatment of male- to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes*. 2005 Dec;113(10):586-92. PMID: 16320157.

Djordjevic ML, Stanojevic DS, Bizic MR. Rectosigmoid vaginoplasty: clinical experience and outcomes in 86 cases. *J Sex Med*. 2011 Dec;8(12):3487-94. Epub 2011 Oct 13. PMID: 21995738.

Djordjevic ML, Bizic MR. Comparison of two different methods for urethral lengthening in female to male (metoidioplasty) surgery. *J Sex Med*. 2013 May;10(5):1431-8. Epub 2013 Feb 27. PMID: 23444841.

Doorduyn T, van Berlo W. Trans people's experience of sexuality in the Netherlands: a pilot study. *J Homosex*. 2014;61(5):654-72. PMID: 24295055.

Doorn CD, Poortinga J, Verschoor AM. Cross-gender identity in transvestites and male transsexuals. *Arch Sex Behav*. 1994 Apr;23(2):185-201. PMID: 8018022.

Doornaert M, Hoebeke P, Ceulemans P, T'Sjoen G, Heylens G, Monstrey S. Penile reconstruction with the radial forearm flap: an update. *Handchir Mikrochir Plast Chir*. 2011 Aug;43(4):208-14. Epub 2011 Aug 11.

A-Dos Ramos Farías MS, Picconi MA, Garcia MN, González JV, Basiletti J, Pando Mde L, Avila MM. Human papilloma virus genotype diversity of anal infection among trans (male to female transvestites, transsexuals or transgender) sex workers in Argentina. *J Clin Virol*. 2011 Jun;51 (2):96-9. Epub 2011 Apr 20. PMID: 21511521.

B-Dos Ramos Farías MS, Garcia MN, Reynaga E, Romero M, Vaulet ML, Fermepín MR, Toscano MF, Rey J, Marone R, Squiquera L, González JV, Basiletti J, Picconi MA, Pando MA, Avila MM. First report on sexually transmitted infections among trans (male to female transvestites, transsexuals, or transgender) and male sex workers in Argentina: high HIV, HPV, HBV, and syphilis prevalence. *Int J Infect Dis*. 2011 Sep;15(9):e635-40. Epub 2011 Jul 13. PMID: 21742530.

DSM: American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, D.C: American Psychiatric Association.

Dubois L. Associations between transition-specific stress experience, nocturnal decline in ambulatory blood pressure, and C-reactive protein levels among transgender men. *Am J Hum Biol* 2012 Jan- Feb;24(1):52-61. Epub 2011 Nov 28. PMID: 22120883.

Duisin D, Nikolić-Balkoski G, Batinić B. Sociodemographic profile of transsexual patients. *Psychiatr Danub*. 2009 Jun;21(2):220-3. PMID: 19556952.

Duišin D, Batinić B, Barišić J, Djordjevic ML, Vujović S, Bizic M. Personality disorders in persons with gender identity disorder. *ScientificWorldJournal*. 2014;2014:809058. Epub 2014 May 13. PMID: 24959629.

Dunn, OJ. Multiple Comparisons Among Means. *J Am Statis Assoc*. 1961 Mar; 56(293): 52- 64. (Not in PubMed) www.jstor.org/stable/2282330.

Elamin M, Garcia M, Murad M, Erwin P, Montori V. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)*. 2010 Jan;72 (1):1-10. Epub 2009 May 16. PMID: 19473174.

Elaut E, Bogaert V, De Cuypere G, Weyers S, Gijs L, Kaufman J, T'Sjoen G. Contribution of androgen receptor sensitivity to the relation between testosterone and sexual desire: An exploration in male-to-female transsexuals. *J Endocrinol Invest*. 2010 Jan;33(1):37-41. Epub 2009 Jul 20. PMID: 19620824.

Ettner R. Care of the elderly transgender patient. *Curr Opin Endocrinol Diabetes Obes* 2013 Dec;20 (6):580-4. PMID: 24468762.

Europe QOL 2010 Anderson R, Mikulić B, Vermeylen G, Lyly-Yrjanainen M, Zigante V. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work -Overview*. EF0902. December 13, 2010. www.eurofound.europa.eu/publications/report/2009/quality-of-life/second-european-quality-of-life-survey-overview.

Europe QOL 2011 Kotowska IE, Matysiak A, Styrac M, Pailhe A, Solaz, A Vignoli D. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work*. EF1002. August 22, 2011. NLM classification: WC 503.6. www.eurofound.europa.eu/publications/report/2010/quality-of-life-social-policies/second-european-quality-of-life-survey-family-life-and-work.

Fares WH. The 'availability' bias: underappreciated but with major potential implications. *Crit Care*. 2014 Mar 12;18(2):118. PMID: 25029621.

Ferring D, Filipp SH. Messung des Selbstwertgefühls: Befunde zu Reliabilität, Validität und Stabilität der Rosenberg-Skala [Measurement of self-esteem: Findings on reliability, validity, and stability of the Rosenberg Scale]. *Diagnostica*. 1996; 42: 284-292. German. (Not in PubMed)

Ferron P, Young S, Boulanger C, Rodriguez A, Moreno J. Integrated care of an aging HIV-infected male-to-female transgender patient. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):278-82. Epub 2010 Mar 19. PMID: 20303795.

Fisher AD, Bandini E, Casale H, Ferruccio N, Meriggiola MC, Gualerzi A, Manieri C, Jannini E, Mannucci E, Monami M, Stomaci N, Delle Rose A, Susini T, Ricca V, Maggi M. Sociodemographic and clinical features of gender identity disorder: an Italian multicentric evaluation. *J Sex Med*. 2013 Feb;10(2):408-19. Epub 2012 Nov 21. PMID: 23171237.

Fleming M, Steinman C, Bocknek G. Methodological problems in assessing sex-reassignment surgery: a reply to Meyer and Reter. *Arch Sex Behav*. 1980 Oct;9(5):451-6. PMID: 7447685.

Fleming M, Cohen D, Salt P, Jones D, Jenkins S. A study of pre- and postsurgical transsexuals: MMPI characteristics. *Arch Sex Behav*. 1981 Apr;10(2):161-70. PMID: 7247725.

Flores A, Herman J, Gates G, Brown T. (2016) *How many adults identify as transgender in the United States?* Los Angeles, CA: The Williams Institute.

Frances AJ, Nardo JM. ICD-11 should not repeat the mistakes made by DSM-5. *Br J Psychiatry*. 2013 Jul;203(1):1-2. PMID: 23818530.

Frade-Costa EM, Bilharinho Mendonca B. Clinical management of transsexual subjects. *Arq Bras Endocrinol Metab*. 2014;58(2):188-96. (Not in PubMed)

Franco T, Miranda L, Franco D, Zaidhaft S, Aran M. Male-to-female transsexualsurgery: experience at the UFRJ University Hospital. *Rev Col Bras Cir*. 2010 Dec;37(6):426-34. PMID: 21340258.

Fuss J, Biedermann S, Stalla G, Auer M. On the quest for a biomechanism of transsexualism: is there a role for BDNF? *J Psychiatr Res*. 2013 Dec;47(12):2015-7. Epub 2013 Sep 7. PMID: 23915300.

Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav*. 1998 Apr;27(2):209-26. PMID: 9562902.

Garaffa G, Gentile V, Antonini G, Tsafrakidis P, Raheem AA, Ralph DJ. Penile reconstruction in the male. *Arab J Urol*. 2013 Sep;11(3):267-71. Epub 2013 Jun 12. PMID: 26558091.

Garcia-Falgueras A, Swaab DF. Sexual hormones and the brain: an essential alliance for sexual identity and sexual orientation. *Endocr Dev*. 2010;17:22-35. Epub 2009 Nov 24. PMID: 19955753.

Garcia-Falgueras A, Ligtenberg L, Kruijver FP, Swaab DF. Galanin neurons in the intermediate nucleus (InM) of the human hypothalamus in relation to sex, age, and gender identity. *J Comp Neurol*. 2011 Oct 15;519(15):3061-84. PMID: 21618223.

García-Malpartida K, Martín-Gorgojo A, Rocha M, Gómez-Balaguer M, Hernández-Mijares A. Prolactinoma induced by estrogen and cyproterone acetate in a male-to-female transsexual. *Fertil Steril*. 2010 Aug;94(3):1097.e13-5. Epub 2010 Mar 12. PMID: 20227072.

Garrels L, Kockott G, Michael N, Preuss W, Renter K, Schmidt G, Sigusch V, Windgassen K. Sex ratio of transsexuals in Germany: the development over three decades. *Acta Psychiatr Scand*. 2000 Dec;102(6):445-8. PMID: 11142434.

Gaspari L, Paris F, Philibert P, Audran F, Orsini M, Servant N, Maïmoun L, Kalfa N, Sultan C. 'Idiopathic' partial androgen insensitivity syndrome in 28 newborn and infant males: impact of prenatal exposure to environmental endocrine disruptor chemicals? *Eur J Endocrinol*. 2011 Oct;165 (4):579-87. Epub 2011 Jul 25. PMID: 21788424.

Gates GJ. How many people are lesbian, gay, bisexual, and transgender? 2011. (Not in PubMed)
williamsinstitute@law.ucla.edu.

Giami A, Le Bail J. HIV infection and STI in the trans population: a critical review. *Rev Epidemiol Sante Publique*. 2011 Aug;59(4):259-68. Epub 2011 Jul 20. PMID: 21767925.

Glezer A, McNiel D, Binder R. Transgendered and incarcerated: a review of the literature, current policies and laws, and ethics. *J Am Acad Psychiatry Law*. 2013;41(4):551-9. PMID: 24335329.

A-Goddard JC, Vickery RM, Terry TR. Development of feminizing genitoplasty for gender dysphoria. *J Sex Med*. 2007 Jul;4(4 Pt 1):981-9. Epub 2007 Apr 19. PMID: 17451484.

B-Goddard JC, Vickery RM, Qureshi A, Summerton DJ, Khoosal D, Terry TR. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. *BJU Int*. 2007 Sep;100(3):607-13. PMID: 17669144.

Godlewski J. Transsexualism and anatomic sex ratio reversal in Poland. *Arch Sex Behav*. 1988 Dec;17(6):547-8. PMID: 3265612.

Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. *Br Med J*. 1970 May 23;1(5707):439-43. PMID: 5420206.

Goldman M. Spring 2008 - Stat C141/ Bioeng C141 - Statistics for Bioinformatics. Course Website: <http://www.stat.berkeley.edu/users/hhuang/141C-2008.html>. Section Website: <http://www.stat.berkeley.edu/users/mgoldman>.

Gómez-Gil E, Trilla García A, Godás Sieso T, Halperin Rabinovich I, Puig Domingo M, Vidal Hagemeyer A, Peri Nogués JM. Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand. *Actas Esp Psiquiatr*. 2006 Sep-Oct;34(5):295-302. Spanish. PMID: 17117339.

Gómez-Gil E, Vidal-Hagemeyer A, Salamero M. MMPI-2 characteristics of transsexuals requesting sex reassignment: comparison of patients in pre-hormonal and presurgical phases. *J Pers Assess*. 2008 Jul;90(4):368-74. PMID: 18584445.

Gómez-Gil E, Esteva I, Almaraz M, Pasaro E, Segovia S, Guillamon A. Familiality of gender identity disorder in non-twin siblings. *Arch Sex Behav*. 2010 Apr;39(2):546-52. Epub 2009 Jul 29. PMID: 19639402.

Gómez-Gil E, Esteva I, Carrasco R, Almaraz MC, Pasaro E, Salamero M, Guillamon A. Birth order and ratio of brothers to sisters in Spanish transsexuals. *Arch Sex Behav*. 2011 Jun;40(3):505-10. Epub 2010 Mar 16. PMID: 20232130.

A-Gómez-Gil E, Gómez A, Cañizares S, Guillamón A, Rametti G, Esteva I, Vázquez A, Salamero- Baró M. Clinical utility of the Bem Sex Role Inventory (BSRI) in the Spanish transsexual and nontranssexual population. *J Pers Assess*. 2012;94(3):304-9. Epub 2012 Jan 13. PMID: 22242861.

B-Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*. 2012 May;37(5):662-70. Epub 2011 Sep 19. PMID: 21937168.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Qual Life Res*. 2014 Mar;23(2):669-76. Epub 2013 Aug 13. PMID: 23943260.

Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res*. 2005;64 Suppl 2:31-6. PMID: 16286768.

Gooren L. Clinical practice. Care of transsexual persons. *N Engl J Med*. 2011 Mar 31;364(13):1251-7. PMID: 21449788.

A-Gooren L, Giltay E. Men and women, so different, so similar: observations from cross-sex hormone treatment of transsexual subjects. *Andrologia*. 2014 Jun;46(5):570-5. Epub 2013 May 19. PMID: 23682909.

B-Gooren L. Management of female-to-male transgender persons: medical and surgical management, life expectancy. *Curr Opin Endocrinol Diabetes Obes.* 2014 Jun;21(3):233-8. PMID: 24755998.

C-Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross- sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. *Eur J Endocrinol.* 2014 Jun;170(6):809-19. Epub 2014 Mar 10. PMID: 24616414.

D-Gooren L, Lips P. Conjectures concerning cross-sex hormone treatment of aging transsexual persons. *J Sex Med.* 2014 Aug;11(8):2012-9. Epub 2014 Apr 29. PMID: 24775178.

E-Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia.* 2014 Dec;46(10):1156-60. Epub 2013 Dec 12. PMID: 24329588.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebleux S, Penochet J, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lançon C, Bonierbale M. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med.* 2012 Feb;9 (2):531-41. Epub 2011 Dec 6. PMID: 22145968.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet J, Pringuey D, Albarel F, Morange I, Bonierbale M, Lançon C, Auquier P. Hormonal therapy is associated with better self- esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis.* 2013 Nov;201(11):996-1000. PMID: 24177489.

Grant JE, Flynn M, Odlaug BL, Schreiber LR. Personality disorders in gay, lesbian, bisexual, and transgender chemically dependent patients. *Am J Addict.* 2011 Sep-Oct;20(5):05-11. Epub 2011 Jul 18. PMID: 21838838.

Green R. Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res.* 1998 May;10 Suppl 1:S22-4. PMID: 9669217.

Greenberg G, Frank G. Response set in the Tennessee Department of Mental Health Self Concept Scale. *J Clin Psychol.* 1965 Jul;21:287-8. PMID: 14332192.

Greenberg RP, Laurence L. A comparison of the MMPI results for psychiatric patients and male applicants for transsexual surgery. *J Nerv Ment Dis.* 1981 May;169(5):320-3. PMID: 7217944.

Gurtman MB. Interpersonal Problems and the Psychotherapy Context: The Construct Validity of the Inventory of Interpersonal Problems. *Psychological Assessment.* 1996; 8 (3):241-55. (Not in PubMed)

Guadamuz TE, Wimonasate W, Varangrat A, Phanuphak P, Jommaroeng R, McNicholl JM, Mock PA, Tappero JW, van Griensven F. HIV prevalence, risk behavior, hormone use and surgical history among transgender persons in Thailand. *AIDS Behav.* 2011 Apr;15(3):650-8. PMID: 21104008.

A-Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008 Apr 26;336(7650):924-6. PMID: 18436948.

B-Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ.* 2008 May 3;336 (7651):995-8. PMID: 18456631.

C-Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. *BMJ.* 2008 May 10;336(7652): 1049-51. Erratum in: *BMJ.* 2008 Jun 21;336(7658). PMID: 18467413.

A-Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol.* 2011 Apr;64(4):395-400. Epub 2010 Dec 30. PMID: 21194891.

B-Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence study limitations (risk of bias). *J Clin Epidemiol.* 2011 Apr;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017. Epub 2011 Jan 19. PMID: 21247734.

C-Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Wilt TJ, Moher D, Norris S, Meerpohl J, Schünemann HJ, GRADE Working Group. GRADE guidelines: 6. Rating the quality of evidence publication bias. *J Clin Epidemiol*. 2011 Dec;64 (12):1277-82. Epub 2011 Jul 30. PMID: 21802904.

D-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence inconsistency. *J Clin Epidemiol*. 2011 Dec;64(12):1294-302. Epub 2011 Jul 31. PMID: 21803546.

E-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence indirectness. *J Clin Epidemiol*. 2011 Dec;64(12):1303-10. Epub 2011 Jul 30. PMID: 21802903.

Haas AP, Eliason M, Mays VM, Mathy RM, Cochran SD, D'Augelli AR, Silverman MM, Fisher PW, Hughes T, Rosario M, Russell ST, Malley E, Reed J, Litts DA, Haller E, Sell RL, Remafedi G, Bradford J, Beautrais AL, Brown GK, Diamond GM, Friedman MS, Garofalo R, Turner MS, Hollibaugh A, Clayton PJ. Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: review and recommendations. *J Homosex*. 2011;58(1):10-51. PMID: 21213174.

Hage JJ, De Graaf FH. Addressing the ideal requirements by free flap phalloplasty: some reflections on refinements of technique. *Microsurgery*. 1993;14(9):592-8. PMID: 8289643.

Hage JJ, Karim RB. Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plast Reconstr Surg*. 2000 Mar;105(3):1222-7. PMID: 10724285.

Hale JC. Ethical problems with the mental health evaluation standards of care for adult gender variant prospective patients. *Perspectives in Biology and Medicine*. 2007Autumn;50(4):491-505. (Not in PubMed)

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatr Scand*. 2000 Oct;102(4):276- 81. PMID: 11089727.

Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphisms associated with male-to-female transsexuals. *J Clin Psychol*. 2009 Jan;17(1):93-5. Epub 2008 Oct 28. PMID: 18962445.

Hathaway S, Briggs P. Some normative data on new MMPI scales. *J Clin Psychol*. 1957 Oct;13 (4):364-8. PMID: 13463138.

Hathaway SR, Reynolds PC, Monachesi ED. Follow-up of the later careers and lives of 1,000 boys who dropped out of high school. *J Consult Clin Psychol*. 1969 Jun;33(3):370-80. PMID: 4389336.

Hebbar S, Pandey H, Chawla A. Understanding King's Health Questionnaire (KHQ) in assessment of female urinary incontinence. *Int J Res Med Sci* 2015;3:531-8.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94:3132-54. PMID: 19509099.

Hembree WC. Guidelines for pubertal suspension and gender reassignment for transgender adolescents. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):725-32. PMID: 22051008.

Hepp U, Klaghofer R, Burkhard-Kübler R, Buddeberg C. [Treatment follow-up of transsexual patients. A catamnestic study]. *Nervenarzt*. 2002 Mar;73(3):283-8. German. PMID: 11963265.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. *J Psychosom Res*. 2005 Mar;58(3):259-61. PMID: 15865950.

Herbst J, Jacobs E, Finlayson T, McKleroy V, Neumann M, Crepaz N. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. *AIDS Behav*. 2008 Jan;12(1):1-17. Epub 2007 Aug 13. PMID: 17694429.

Heresová J, Pobisová Z, Hampl R, Stárka L. Androgen administration to transsexual women. II. Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int*. 2014 Nov 21;111(47):795-801. PMID: 25487762.

A-Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med*. 2014 Jan;11(1):119-26. Epub 2013 Oct 28. PMID: 24344788.

B-Heylens G, Elaut E, Kreukels BP, Paap MC, Cerwenka S, Richter-Appelt H, Cohen-Kettenis PT, Haraldsen I, De Cuypere G. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. *Br J Psychiatry*. 2014 Feb;204(2):151-6. Epub 2013 May 9. PMID: 23869030.

HHS-HP: US Department of Health and Human Services. Lesbian, gay, bisexual and transgender health: objectives. Healthy People 2020. www.healthypeople.gov/2020/topics/objectives2020/overview.aspx?topicid=25.

HHS-2011: US Department of Health and Human Services. Affordable Care Act to improve data collection, reduce health disparities. www.hhs.gov/news/press/2011pres/06/20110629a.html.

Hines M, Ahmed SF, Hughes IA. Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. *Arch Sex Behav*. 2003 Apr;32(2):93-101. PMID: 12710824.

Hoekzema E, Schagen SE, Kreukels BP, Veltman DJ, Cohen-Kettenis PT, Delemarre-van de Waal H, Bakker J. Regional volumes and spatial volumetric distribution of gray matter in the gender dysphoric brain. *Psychoneuroendocrinology*. 2015 May;55:59-71. Epub 2015 Jan 30. PMID: 25720349.

Hoenig J, Kenna J, Youd A. A follow-up study of transsexualists: social and economic aspects. *Psychiatr Clin (Basel)*. 1970;3(2):85-100. PMID: 5424767.

Hoenig J, Kenna JC, Youd A. Surgical treatment for transsexualism. *Acta Psychiatr Scand*. 1971;47 (1):106-33 or 36. PMID: 5096332 or 5148350.

Hoenig J, Kenna J. Epidemiological aspects of transsexualism. *Psychiatr Clin (Basel)*. 1973;6(2):65- 80. PMID: 4705331.

Hoffman B. An Overview of Depression among Transgender Women. *Depress Res Treat*. 2014;2014:394283. Epub 2014 Mar 13. PMID: 24744918.

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009 Jan 21; (1):MR000006. PMID: 19160345.

Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ*. 2010 Mar 23;340:c723. PMID: 20332510.

Hopewell S, Hirst A, Collins GS, Mallett S, Yu LM, Altman DG. Reporting of participant flow diagrams in published reports of randomized trials. *Trials*. 2011 Dec 5;12:253. PMID: 22141446.

Horbach S, Bouman M, Smit J, Özer M, Buncamper M, Mullender M. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med*. 2015 Jun;12(6):1499-512. Epub 2015 Mar 26. PMID: 25817066.

Horowitz LM, Rosenberg SE, Baer BA, Ureño G, Villaseñor VS. Inventory of interpersonal problems: psychometric properties and clinical applications. *J Consult Clin Psychol*. 1988 Dec;56 (6):885-92. PMID: 3204198.

Hoshiai M, Matsumoto Y, Sato T, Ohnishi M, Okabe N, Kishimoto Y, Terada S, Kuroda S. Psychiatric comorbidity among patients with gender identity disorder. *Psychiatry Clin Neurosci*. 2010 Oct;64(5):514-9. Epub 2010 Aug 19. PMID: 20727112.

A-Hunt DD, Hampson JL. Follow-up of 17 biologic male transsexuals after sex-reassignment surgery. *Am J Psychiatry*. 1980 Apr;137(4):432-8. PMID: 7361928.

B-Hunt DD, Hampson JL. Transsexualism: a standardized psychosocial rating format for the evaluation of results of sex reassignment surgery. *Arch Sex Behav*. 1980 Jun;9(3):255-63. PMID: 7396697.

Hunt DD, Carr JE, Hampson JL. Cognitive correlates of biologic sex and gender identity in transsexualism. *Arch Sex Behav*. 1981 Feb;10(1):65-77. PMID: 7011255.

Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, T'Sjoen G. Karyotyping, is it worthwhile in transsexualism? *J Sex Med*. 2011 Feb;8(2):475-8. Epub 2010 Nov 29. PMID: 21114769.

A-Imperato-McGinley J. 5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature. *Adv Exp Med Biol*. 2002;511:121-31; discussion 131-4. PMID: 12575759.

B- Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5 alpha- reductase-2 deficiency. *Mol Cell Endocrinol*. 2002 Dec 30;198(1-2):51-9. PMID: 12573814.

Insel T. Director's Blog: Transforming Diagnosis. April 29, 2013.
<http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml>.

Insel T. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry*. 2014 Apr;171(4):395-7. PMID: 24687194.

IOM 2011 Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. Institute of Medicine (IOM). (Study Sponsor: The National Institutes of Health). The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Issued March 31, 2011. <http://thefenwayinstitute.org/documents/lgbthealthreportbriefembargoed.pdf>.

Jackson PA. Thai research on male homosexuality and transgenderism and the cultural limits of Foucaultian analysis. *J Hist Sex*. 1997 Jul;8(1):52-85. PMID: 11619530.

Jackson, Peter A.. An explosion of Thai identities: peripheral genders and the limits of queer theory. *Culture, Health, & Sexuality*, 2000;2(4):405-24. Taylor & Francis. (Not in PubMed)

Jackson PA. Pre-gay, post-queer: Thai perspectives on proliferating gender/sex diversity in Asia. *J Homosex*. 2001;40(3-4):1-25. PMID: 11386329.

Jacobeit J, Gooren L, Schulte H. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. *Eur J Endocrinol*. 2009 Nov;161(5):795-8. Epub 2009 Sep 11. PMID: 19749027.

Jacobs, S-E, Thomas W, and Lang S (Eds.). (1997). *Two-spirit people: Native American gender identity, sexuality, and spirituality*. Urbana: University of Illinois Press.

Jain A, Bradbeer C. Gender identity disorder: treatment and post-transition care in transsexual adults. *Int J STD AIDS*. 2007 Mar;18(3):147-50. PMID: 17362542.

Jarolím L, Sedý J, Schmidt M, Nanka O, Foltán R, Kawaciuk I. Gender reassignment surgery in male-to-female transsexualism: A retrospective 3-month follow-up study with anatomical remarks. *J Sex Med*. 2009 Jun;6(6):1635-44. Epub 2009 Mar 30. PMID: 19473463.

Jokić-Begić N, Lauri Korajlija A, Jurin T. Psychosocial adjustment to sex reassignment surgery: a qualitative examination and personal experiences of six transsexual persons in Croatia. *Scientific World Journal*. 2014;2014:960745. Epub 2014 Mar 25. PMID: 24790589.

Joseph A, Shabir I, Marumadi E, Dada R, Ammini A, Mehta M. Psychosexual outcomes in three siblings with partial androgen insensitivity syndrome: impact of nature versus nurture. *J Pediatr Endocrinol Metab*. 2013;26(9-10):915-20. PMID: 23729553.

Judge C, O'Donovan C, Callaghan G, Gaoatswe G, O'Shea D. Gender dysphoria - prevalence and co- morbidities in an Irish adult population. *Front Endocrinol (Lausanne)* 2014;5:87. Epub 2014 Jun 13. PMID: 24982651.

Jürgensen M, Hiort O, Holterhus PM, Thyen U. Gender role behavior in children with XY karyotype and disorders of sex development. *Horm Behav*. 2007 Mar;51(3):443-53. Epub 2007 Jan 12. PMID: 17306800.

Keenan JP, Wheeler MA, Gallup GG Jr, Pascual-Leone A. Self-recognition and the right prefrontal cortex. *Trends Cogn Sci*. 2000 Sep;4(9):338-344. PMID: 10962615.

Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol*. 1997 Dec;104(12):1374-9. PMID: 9422015.

Khan L. Transgender health at the crossroads: legal norms, insurance markets, and the threat of healthcare reform. *Yale J Health Policy Law Ethics*. 2011 Summer;11(2):375-418. PMID: 22136012.

Khandelwal A, Agarwal A, Jiloha RC. A 47,XXY female with gender identity disorder. *Arch Sex Behav*. 2010 Oct;39(5):1021-3. PMID: 20464469.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. *Arch Sex Behav*. 1987 Dec;16(6):511-22. PMID: 3426393.

Kockott G, Fahrner EM. Male-to-female and female-to-male transsexuals: a comparison. *Arch Sex Behav*. 1988 Dec;17(6):539-46. PMID: 3223814.

Kohlberg, L. "A Cognitive-Developmental Analysis of Children's Sex-Role Concepts and Attitudes." In E. E. Maccoby (ed.). *The Development of Sex Differences*. Stanford, Calif.: Stanford University Press, 1966.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. *Psychopathology*. 2008;41(2):96-100. Epub 2007 Nov 23. PMID: 18033979.

Krege S, Bex A, Lümnen G, Rübber H. Male-to-female transsexualism: a technique, results and long-term follow-up in 66 patients. *BJU Int*. 2001 Sep;88(4):396-402. PMID: 11564029.

Kreukels B, Haraldsen, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis P. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry*. 2012 Aug;27(6):445-50. Epub 2010 Jul 9. PMID: 20620022.

Kröhn W, Bertermann H, Wand H, Wille R. [Transsexualism: a long-term follow-up after sex reassignment surgery (author's transl)]. *Nervenarzt*. 1981 Jan;52(1):26-31. PMID: 7219610.

Kronawitter D, Gooren LJ, Zollver H, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. Effects of transdermal testosterone or oral dydrogesterone on hypoactive sexual desire disorder in transsexual women: results of a pilot study. *Eur J Endocrinol*. 2009 Aug;161(2): 363-8. Epub 2009 Jun 4. PMID: 19497984.

Kruijver FP, Fernández-Guasti A, Fodor M, Kraan EM, Swaab DF. Sex differences in androgen receptors of the human mamillary bodies are related to endocrine status rather than to sexual orientation or transsexuality. *J Clin Endocrinol Metab*. 2001 Feb;86(2):818-27. PMID: 11158052.

Kuiper B, Cohen-Kettenis P. Sex reassignment surgery: a study of 141 Dutch transsexuals. *Arch Sex Behav*. 1988 Oct;17(5):439-57. PMID: 3219066.

Kuhn A, Hildebrand R, Birkhäuser M. Do transsexuals have micturition disorders? *Eur J Obstet Gynecol Reprod Biol*. 2007 Apr;131(2):226-30. Epub 2006 May 5. PMID: 16678333.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril*. 2009 Nov;92(5):1685-1689.e3. Epub

2008 Nov 6. PMID: 18990387.

Kuhn A, Santi A, Birkhäuser M. Vaginal prolapse, pelvic floor function, and related symptoms 16 years after sex reassignment surgery in transsexuals. *Fertil Steril*. 2011 Jun;95(7):2379-82. Epub 2011 Apr 2. PMID: 21458798.

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ*. 1998 Oct 31;317(7167):1185-90. PMID: 9794851.

Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):MR000012. Update in: *Cochrane Database Syst Rev*. 2011; (4) MR000012. PMID: 17443633.

Kupfer DJ, Kuhl EA, Regier DA. Two views on the new DSM-5: DSM-5: a diagnostic guide relevant to both primary care and psychiatric practice. *Am Fam Physician*. 2013 Oct 15;88(8):Online. PMID: 24364581.

Lader EW, Cannon CP, Ohman EM, Newby LK, Sulmasy DP, Barst RJ, Fair JM, Flather M, Freedman JE, Frye RL, Hand MM, Jesse RL, Van de Werf F, Costa F; American Heart Association. The clinician as investigator: participating in clinical trials in the practice setting: Appendix 2: statistical concepts in study design and analysis. *Circulation*. 2004 Jun 1;109(21):e305-7. PMID: 15173053.

Lament C. Transgender Children: Conundrums and Controversies A Introduction to the Section. *Psychoanal Study Child* 2014;68:13-27. PMID: 26173324.

Lancet Editorial-No Authors . Health of lesbian, gay, bisexual, and transgender populations. *Lancet*. 2011 April 9;377: 1211. PMID:2 1481690.

A - Landén M, Wålinder J, Lambert G, Lundström B. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand*. 1998 Apr;97(4):284-9. PMID: 9570489.

B – Landén M, Walinder J, Lundstrom B. Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. *Acta Psychiatr Scand* 1998: 97: 189-194.

Lang, S. (1998). *Men as Women, Women as Men: Changing Gender in Native American Cultures*. Austin, TX: University of Texas Press.

Lang RJ, Vernon PE. Dimensionality of the perceived self: the Tennessee Self Concept Scale. *Br J Soc Clin Psychol*. 1977 Nov;16(4):363-71. PMID: 588892.

Lawrence AA. Changes in sexual orientation in six male-to-female (MtF) transsexuals. *Arch Sex Behav*. 1999 Dec;28(6):581-3. PMID:> 10650442.

Lawrence A. Sexuality before and after male-to-female sex reassignment surgery. *Arch Sex Behav.* 2005 Apr;34(2):147-66. PMID: 15803249.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Arch Sex Behav.* 2006 Dec;35(6):717-27. Epub 2006 Nov 16. PMID: 17109225.

A-Lawrence AA. Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. *Arch Sex Behav.* 2010 Apr;39(2):514-45. Epub 2010 Feb 6. PMID: 20140487.

B-Lawrence AA. Societal individualism predicts prevalence of nonhomosexual orientation in male- to-female transsexualism. *Arch Sex Behav.* 2010 Apr;39(2):573-83. Epub 2008 Dec 9. PMID: 19067152.

Leavitt F, Berger JC, Hoeppner JA, Northrop G. Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis.* 1980 Nov;168(11):693-7. PMID: 6255090.

A-Leclère F, Casoli V, Weigert R. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med.* 2015 Jul;12(7):1655-6. Epub 2015 Jun 11. PMID: 26096230.

B-Leclère FM, Casoli V, Weigert R. Vaginoplasty in Male-to-Female Transsexual Surgery: A Training Concept Incorporating Dissection Room Experience to Optimize Functional and Cosmetic Results. *J Sex Med.* 2015 Oct;12(10):2074-83. PMID: 26481600.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. *Endocr Pract.* 2013 Jul-Aug;19(4):644-50. PMID: 23512380.

Lindemalm G, Körlin D, Uddenberg N. Long-term follow-up of "sex change" in 13 male-to-female transsexuals. *Arch Sex Behav*. 1986 Jun;15(3):187-210. PMID: 3729700.

Lindemalm G, Körlin D, Uddenberg N. Prognostic factors vs. outcome in male-to-female transsexualism. A follow-up study of 13 cases. *Acta Psychiatr Scand*. 1987 Mar;75(3):268-74. PMID: 3591409.

Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav*. 1975 Nov;4(6):639-56. PMID: 1212093.

Lioudaki E, Ganotakis ES, Mikhailidis DP, Nair DR. The estrogenic burden on vascular risk in male- to-female transsexuals. *Curr Pharm Des*. 2010;16(34):3815-22. PMID: 21128891

Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, da Graça Borges Fortes M, Petry AR, Silveira E, Henriques AA. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. *Arch Sex Behav*. 2006 Dec;35(6):711-5. PMID: 17075731.

Lothstein LM. The aging gender dysphoria (transsexual) patient. *Arch Sex Behav*. 1979 Sep;8 (5):431-44. PMID: 496624.

Lothstein LM, Roback H. Black female transsexuals and schizophrenia: a serendipitous finding? *Arch Sex Behav*. 1984 Aug;13(4):371-86. PMID: 6487080.

Lothstein LM. Psychological testing with transsexuals: a 30-year review. *J Pers Assess*. 1984 Oct;48 (5):500-7. PMID: 6389823.

Maccoby EE. The role of gender identity and gender constancy in sex-differentiated development. *New Dir Child Dev*. 1990 Spring;(47):5-20. PMID: 2194142.

Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, Cartigny M, Pienkowski C, Polak M, Skordis N, Mazen I, Ocal G, Berberoglu M, Reynaud R, Baumann C, Cabrol S, Simon D,

Kayemba-Kay's K, De Kerdanet M, Kurtz F, Leheup B, Heinrichs C, Tenoutasse S, Van Vliet G, Grüters A, Eunice M, Ammini AC, Hafez M, Hochberg Z, Einaudi S, Al Mawlawi H, Nuñez CJ, Servant N, Lumbroso S, Paris F, Sultan C. Phenotypical, biological, and molecular heterogeneity of 5 α -reductase deficiency: an extensive international experience of 55 patients. *J Clin Endocrinol Metab*. 2011 Feb;96(2):296-307. Epub 2010 Dec 8. PMID: 21147889.

Marks I, Green R, Mataix-Cols D. Adult gender identity disorder can remit. *Compr Psychiatry*. 2000 Jul-Aug;41(4):273-5. PMID: 10929795.

Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: A systematic review of the literature. *Int Rev Psychiatry*. 2015 Sep 2;1-12. [Epub ahead of print]. PMID: 26329283.

Matarazzo B, Barnes S, Pease J, Russell L, Hanson J, Soberay K, Gutierrez P. Suicide risk among lesbian, gay, bisexual, and transgender military personnel and veterans: what does the literature tell us? *Suicide Life Threat Behav*. 2014 Apr;44(2):200-17. Epub 2014 Feb 3. PMID: 24494604.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. *Br J Psychiatry*. 1988 Apr;152:550-3. PMID: 3167409.

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. *Br J Psychiatry*. 1990 Aug;157:261-4. PMID: 2224377.

McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993 Mar;31(3):247-63. PMID: 8450681.

McHugh PR, Slavney PR. Mental illness comprehensive evaluation or checklist? *N Engl J Med*. 2012 May 17;366(20):1853-5. PMID: 22591291.

Meads C, Pennant M, McManus J, Bayliss S. West Midlands Health Technology Assessment Collaboration. A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. *Health Technology Assessment Database*. 2009. No.3. www.birmingham.ac.uk/Documents/college-mds/haps/projects/WMHTAC/REPreports/2009/LGBTHealth030409finalversion.pdf.

Medraś M, Józków P. Transsexualism diagnostic and therapeutic aspects. *Endokrynol Pol*. 2010 Jul-Aug;61(4):412-6. PMID: 20806188.

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. *Sexual and Relationship Therapy*. 2007 Feb; 22(1):77-81. (Not in PubMed)

Melendez RM, Exner TA, Ehrhardt AA, Dodge B, Remien RH, Rotheram-Borus MJ, Lightfoot M, Hong D. Health and health care among male-to-female transgender persons who are HIV positive. *Am J Public Health*. 2006 Jun;96(6):1034-7. Epub 2005 Aug 30. PMID: 16131645.

Mepham N, Bouman W, Arcelus J, Hayter M, Wylie K. People with gender dysphoria who self- prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. *J Sex Med*. 2014 Dec;11(12):2995-3001. Epub 2014 Sep 11. PMID: 25213018.

Meriggiola M, Berra M. Long-term cross-sex hormone treatment is safe in transsexual subjects. *Asian J Androl*. 2012 Nov;14(6):813-4. Epub 2012 Aug 27. PMID: 22922319.

Meriggiola M, Berra M. Safety of hormonal treatment in transgenders. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):565-9. PMID: 24468759.

A-Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):597-606. Epub 2015 Mar 25. PMID: 25692791.

B-Meriggiola MC, Gava G. Endocrine care of transpeople part II. A review of cross-sex hormonal treatments, outcomes and adverse effects in transwomen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):607-15. Epub 2015 Mar 25. PMID: 25692882.

Meyer J, Knorr N, Blumer D. Characterization of a self-designated transsexual population. *Arch Sex Behav*. 1971 Sep;1(3):219-30. PMID: 24179067.

A-Meyer JK. Sex assignment and reassignment: intersex and gender identity disorders. Foreword. *Clin Plast Surg*. 1974 Apr;1(2):199-200. PMID: 4426156.

B-Meyer JK. Psychiatric considerations in the sexual reassignment of non-intersex individuals. *Clin Plast Surg*. 1974 Apr;1(2):275-83. PMID: 4426161.

C-Meyer JK, Hoopes JE. The gender dysphoria syndromes. A position statement on so-called "transsexualism". *Plast Reconstr Surg*. 1974 Oct;54(4):444-51. PMID: 4416283.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. *Arch Gen Psychiatry*. 1979 Aug;36(9): 1010-5. PMID: 464739.

Meyer WJ, Finkelstein JW, Stuart CA, Webb A, Smith ER, Payer AF, Walker PA. Physical and hormonal evaluation of transsexual patients during hormonal therapy. *Arch Sex Behav*. 1981 Aug;10 (4):347-56. PMID: 6794543.

Meyer WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav* 1986 Apr;15(2):121-38. PMID: 22051002.

Meyer-Bahlburg HF. Gender outcome in 46,XY complete androgen insensitivity syndrome: comment on T'Sjoen et al. (2010). *Arch Sex Behav*. 2010 Dec;39(6):1221-4. PMID: 20552263.

Meyer-Bahlburg HF. Gender monitoring and gender reassignment of children and adolescents with a somatic disorder of sex development. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):639-49. PMID: 22051002. Epub 2011 Sep 23.

Miach PP, Berah EF, Butcher JN, Rouse S. Utility of the MMPI-2 in assessing gender dysphoric patients. *J Pers Assess*. 2000 Oct;75(2):268-79. PMID: 11020144.

Michel A, Mormont C, Legros JJ. A psycho-endocrinological overview of transsexualism. *Eur J Endocrinol*. 2001 Oct;145(4):365-76. PMID: 11580991.

Michel A, Ansseau M, Legros J, Pitchot W, Cornet J, Mormont C. Comparisons of two groups of sex-change applicants based on the MMPI. *Psychol Rep* 2002 Aug;91(1):233-40. PMID: 12353786.

Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*. 2003; May-June. Report 33, No. 3: 19-28. PMID: 12854452.

Miller FG. Equipoise and the Ethics of Clinical Research Revisited. *The American Journal of Bioethics*. 2006; 6:4, 59-61. PMID: 16885110.

Miller PB, Weijer C. Trust based obligations of the state and physician-researchers to patient- subjects. *J Med Ethics*. 2006 Sep;32(9):542-7. PMID: 16943338.

A-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010 Mar 23;340:c869. PMID: 20332511.

B-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG; Consolidated Standards of Reporting Trials Group. CONSORT 2010 Explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010 Aug;63(8):e1-37. Epub 2010 Mar 25. Erratum in *J Clin Epidemiol*. 2012 Mar;65(3):351. PMID: 20346624.

Monstrey S, Hoebeke P, Selvaggi G, Ceulemans P, Van Landuyt K, Blondeel P, Hamdi M, Roche N, Weyers S, De Cuypere G. Penile reconstruction: is the radial forearm flap really the standard technique? *Plast Reconstr Surg*. 2009 Aug;124(2):510-8. PMID: 19644267.

Monstrey S, Ceulemans P, Hoebeke P. Sex Reassignment Surgery in the Female-to-Male Transsexual. *Semin Plast Surg*. 2011 Aug;25(3):229-44. PMID: 22851915.

Moreno-Pérez O, Esteva De Antonio I; Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). [Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN)]. *Endocrinol Nutr*. 2012 Jun-Jul;59(6):367-82. Epub 2012 Apr 26. PMID: 22586086. PageID 1330

Moser C. Blanchard's Autogynephilia Theory: a critique. *J Homosex*. 2010;57(6):790-809. PMID: 20582803.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. *J Sex Med*. 2012 Mar;9(3):743-50. Epub 2011 Dec 21. PMID: 22188877.

Motmans J, Ponnet K, De Cuypere G. Sociodemographic characteristics of trans persons in Belgium: A secondary data analysis of medical, state, and social data. *Arch Sex Behav*. 2015 Jul;44(5):1289-99. Epub 2014 Oct 10. PMID: 25300904.

Mueller A, Haeberle L, Zollner H, Claassen T, Kronawitter D, Oppelt P, Cupisti S, Beckmann M, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med*. 2010 Sep;7(9):3190-8. PMID: 20584125.

Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010 Feb;72(2):214-31. Epub 2009 May 16. PMID: 19473181.

Nanda S. The hijras of India: cultural and individual dimensions of an institutionalized third gender role. *J Homosex*. 1985 Summer;11(3-4):35-54. PMID: 4093603.

Nanda, S. (1999). *Neither man nor woman: The hijras of India*. Belmont, CA: Wadsworth Publishing.

Nanda S. (2014, 2nd edition) *Gender Diversity: Cross cultural variations*. Long Grove, IL: Waveland Press.

NIH-LGBT 2013: National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf.

Nemoto T, Iwamoto M, Perngparn U, Areesantichai C, Kamitani E, Sakata M. HIV-related risk behaviors among kathoey (male-to-female transgender) sex workers in Bangkok, Thailand. *AIDS Care*. 2012;24(2):210-9. Epub 2011 Jul 25. PMID: 21780964.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. *Qual Life Res*. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. PMID: 16758113.

Newsom J. Latent variable. *USP 655 SEM. Winter 2015*. (Portland State quantitative methods)www.upa.pdx.edu/IOA/newsom/semclass/ho_latent.pdf.

Nieder T, Herff M, Cerwenka S, Preuss W, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Richter-Appelt H. Age of onset and sexual orientation in transsexual males and females. *J Sex Med*. 2011 Mar;8(3):783-91. Epub 2010 Dec 8. PMID: 21143416.

Nuttbrock L, Hwahng S, Bockting W, Rosenblum A, Mason M, Macri M, Becker J. Lifetime risk factors for HIV/sexually transmitted infections among male-to-female transgender persons. *J Acquir Immune Defic Syndr*. 2009 Nov 1;52(3):417-21. PMID: 19550351.

Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. Gender abuse, depressive symptoms, and HIV and other sexually transmitted infections among male-to-female transgender persons: a three-year prospective study. *Am J Public Health* 2013 Feb;103(2):300-7. Epub 2012 Jun 14. Erratum in: *Am J Public Health*. 2015 Feb;105(2):e5. PMID: 22698023.

NZHTA 2002: Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. Feb-Apr 2002

Odgaard-Jensen J, Vist GE, Timmer A, Kunz R, Akl EA, Schünemann H, Briel M, Nordmann AJ, Pregno S, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2011 Apr 13;(4):MR000012. PMID: 21491415.

O’Gorman EC. A preliminary report on transsexualism in Northern Ireland. *Ulster Med J*. 1981;50 (1):46–9. PMID: 7233635.

Okabe N, Sato T, Matsumoto Y, Ido Y, Terada S, Kuroda S. Clinical characteristics of patients with gender identity disorder at a Japanese gender identity disorder clinic. *Psychiatry Res*. 2008 Jan 15;157 (1-3):315-8. Epub 2007 Oct 23. PMID: 17959255.

Olson J, Forbes C, Belzer M. Management of the transgender adolescent. *Arch Pediatr Adolesc Med*. 2011 Feb;165(2):171-6. PMID: 21300658.

Olsson SE, Jansson I, Moller A. Men as women. Experiences from five case after administrative, hormonal, and surgical treatment. *Nord J Psychiatry*. 1996;50(5):395-9. (Not in PubMed)

Olsson S, Möller A. On the incidence and sex ratio of transsexualism in Sweden, 1972-2002. *Arch Sex Behav*. 2003 Aug;32(4):381-6. PMID: 12856899.

Olsson S, Möller A. Regret after sex reassignment surgery in a male-to-female transsexual: a long- term follow-up. *Arch Sex Behav*. 2006 Aug;35(4):501-6. Epub 2006 Aug 11. PMID: 16900416.

Operario D, Nemoto T. HIV in transgender communities: syndemic dynamics and a need for multicomponent interventions. *J Acquir Immune Defic Syndr*. 2010 Dec;55 Suppl 2:S91-3. PMID: 21406995.

Orel N. Investigating the needs and concerns of lesbian, gay, bisexual, and transgender older adults: the use of qualitative and quantitative methodology. *J Homosex*. 2014;61(1):53-78. PMID: 24313253.

Oster JM, Shastri P, Geyer C. Cerebral venous sinus thrombosis after gender reassignment surgery. *Gend Med*. 2010 Jun;7(3):270-5. PMID: 20638632.

Ott J, van Trotsenburg M, Kaufmann U, Schrögendorfer K, Haslik W, Huber JC, Wenzl R. Combined hysterectomy/salpingo-oophorectomy and mastectomy is a safe and valuable procedure for female-to- male transsexuals. *J Sex Med*. 2010 Jun;7(6):2130-8. Epub 2010 Mar 3. PMID: 20233279.

Paap MC, Meijer RR, Cohen-Kettenis PT, Richter-Appelt H, de Cuypere G, Kreukels BP, Pedersen G, Karterud S, Malt UF, Haraldsen IR. Why the factorial structure of the SCL-90-R is unstable: comparing patient groups with different levels of psychological distress using Mokken Scale Analysis. *Psychiatry Res*. 2012 Dec 30;200(2-3):819-26. Epub 2012 Apr 9. PMID: 22494703.

Palmer D, Dietsch A, Searl J. Endoscopic and stroboscopic presentation of the larynx in male-to- female transsexual persons. *J Voice*. 2012 Jan;26(1):117-26. Epub 2011 Apr 7. PMID: 21477987.

Palmer JR, Wise LA, Robboy SJ, Titus-Ernstoff L, Noller KL, Herbst AL, Troisi R, Hoover RN. Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology*. 2005 Jul;16 (4):583-6. PMID: 15951681.

Palmer JR, Herbst AL, Noller KL, Boggs DA, Troisi R, Titus-Ernstoff L, Hatch EE, Wise LA, Strohsnitter WC, Hoover RN. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environ Health*. 2009 Aug 18;8:37. PMID: 19689815.

Pauly IB. The current status of the change of sex operation. *J Nerv Ment Dis*. 1968 Nov;147(5):460- 71. PMID: 5726920.

Pauly IB. Outcome of sex reassignment surgery for transsexuals. *Aust N Z J Psychiatry* 1981 Mar;15 (1):45-51. PMID: 6942832.

Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola M. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014 Dec;11(12):3002-11. Epub 2014 Sep 24. PMID: 25250780.

Perez KM, Titus-Ernstoff L, Hatch EE, Troisi R, Wactawski-Wende J, Palmer JR, Noller K, Hoover RN; National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril*. 2005 Dec;84(6):1649-56. PMID: 16359959.

Perrone A, Cerpolini S, Maria Salfi N, Ceccarelli C, De Giorgi L, Formelli G, Casadio P, Ghi T, Pelusi G, Pelusi C, Meriggiola M. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. *J Sex Med*. 2009 Nov;6(11):3193-200. Epub 2009 Jun 29. PMID: 19570144.

Persson D. Unique challenges of transgender aging: implications from the literature. *J Gerontol Soc Work*. 2009 Aug-Sep;52(6):633-46. PMID: 19598043.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 1: conceptual and definitional issues in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jan 13;7:3. PMID: 22243994.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 2: Issues of conservatism and pragmatism in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jul 5;7:8. PMID: 22512887.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue. Part 4: general conclusion. *Philos Ethics Humanit Med*. 2012 Dec 18;7:14. PMID: 23249629.

PRO Guidance 2009: U.S. Department of Health and Human Services; Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). *Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labeling claims. December 2009.* <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf>.

Quirós C, Patrascioiu I, Mora M, Aranda GB, Hanzu FA, Gómez-Gil E, Godás T, Halperin I. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. *Endocrinol Nutr*. 2015 May;62(5):210-6. Epub 2015 Mar 16. PMID: 25790747.

Rachlin Katherine. Factors Which Influence Individual's Decisions When Considering Female-To- Male Genital Reconstructive Surgery. *IJT*. 1999 Jul-Sept;3(3). (Not in PubMed) <http://www.symposion.com/ijt/ijt990302.htm> <http://www.iiav.nl/eazines/web/ijt/97-03/numbers/symposion/ijt990302.htm>

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. *Arch Sex Behav*. 1996 Oct;25(5):515-25. PMID: 8899143.

A-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Segovia S, Gomez Á, Guillamon A. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *J Psychiatr Res*. 2011 Feb;45(2):199-204. Epub 2010 Jun 8. PMID: 20562024.

B-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Zubiarre-Elorza L, Segovia S, Gomez Á, Guillamon A. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *J Psychiatr Res*. 2011 Jul;45(7):949-54. Epub 2010 Dec 30. PMID: 21195418.

Randell J. Indications for reassignment surgery. *Archives of Sexual Behavior*. 1971; 1(2):153-61. (Not in PubMed)

Randell J. (1969). *Pre-operative and post-operative status of transsexuals* (Chapter 26) in Green R, Money J (eds):*Trans-sexualism and Sex reassignment*. Baltimore: Johns Hopkins Press.

Rappaport R. Intersex management: what is achieved and what is needed. Commentary to Thyen et al.: epidemiology and initial management of ambiguous genitalia at birth in Germany (*Horm Res*. 2006;66:195-203). *Horm Res*. 2006;66(4):204-5. Epub 2006 Jul 27. PMID: 16877871.

Reed HM. Aesthetic and functional male to female genital and perineal surgery: feminizing vaginoplasty. *Semin Plast Surg*. 2011 May;25(2):163-74. PMID: 22547974.

Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A. The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Arch Sex Behav*. 1999 Feb;28(1):71-89. PMID: 10097806.

Reisner S, Poteat T, Keatley J, Cabral M, Mothopeng T, Dunham E, Holland C, Max R, Baral S. Global health burden and needs of transgender populations: a review. *Lancet*. Epub 16 June 2016. [http://dx.doi.org/10.1016/S0140-6736\(16\)00684-X](http://dx.doi.org/10.1016/S0140-6736(16)00684-X)

Roback HB, Lothstein LM. The female mid-life sex change applicant: a comparison with younger female transsexuals and older male sex change applicants. *Arch Sex Behav*. 1986 Oct;15(5):401-15. PMID: 3789904.

Roscoe W. (1991). *The Zuni Man-Woman*. Albuquerque: University of New Mexico Press.

Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000 Apr-Jun;26(2):191-208. PMID: 10782451.

Rosenberg, M. (1965). *Society and the Adolescent Self-Image*, Princeton University Press, Princeton.

Ross MW, Wålinder J, Lundström B, Thuwe I. Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia. *Acta Psychiatr Scand*. 1981 Jan;63(1):75-82. PMID: 7234467.

Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Arch Sex Behav*. 1989 Apr;18(2):145-53. PMID: 2712690.

Rubin SO. Sex-reassignment surgery male-to-female. Review, own results and report of a new technique using the glans penis as a pseudoclitoris. *Scand J Urol Nephrol Suppl*. 1993;154:1-28. PMID: 8140401.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. *Arch Sex Behav*. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18. PMID: 25690443.

Russell ST, Ryan C, Toomey RB, Diaz RM, Sanchez J. Lesbian, gay, bisexual, and transgender adolescent school victimization: implications for young adult health and adjustment. *J Sch Health*. 2011 May;81(5):223-30. PMID: 21517860.

Safer J, Tangpricha V. Out of the shadows: it is time to mainstream treatment for transgender patients. *Endocr Pract*. 2008 Mar;14(2):248-50. PMID: 18308667.

Salkind MR. Beck depression inventory in general practice. *J R Coll Gen Pract*. 1969 Nov;18 (88):267-71. PMID: 5350525.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun;66(4):371-2. PMID: 22624747.

Savic I, Garcia-Falgueras A, Swaab DF. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Prog Brain Res*. 2010;186:41-62. PMID: 21094885.

Schaeffer CE. The Kutenai female berdache: Courier, guide, prophetess, and warrior. *Ethnohistory*. 1965;12 (3): 193-236. (Not in PubMed)

Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. *Arch Sex Behav*. 1998 Oct;27(5):475-92. PMID: 9795728.

Schroder M, Carroll RA. New women: Sexological outcomes of male-to-female gender reassignment surgery. *JSET*. 1999;24(3):137-46. (Not in PubMed)

Seal L, Franklin S, Richards C, Shishkareva A, Sinclair C, Barrett J. Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens. *J Clin Endocrinol Metab*. 2012 Dec;97(12):4422-8. Epub 2012 Oct 9. PMID: 23055547.

Selvaggi G, Monstrey S, Ceulemans P, T'Sjoen G, De Cuypere G, Hoebeke P. Genital sensitivity after sex reassignment surgery in transsexual patients. *Ann Plast Surg*. 2007 Apr;58(4):427-33. PMID: 17413887.

Selvaggi G, Bellringer J. Gender reassignment surgery: an overview. *Nat Rev Urol*. 2011 May;8 (5):274-82. Epub 2011 Apr 12. PMID: 21487386.

Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. *Clin Breast Cancer*. 2011 Dec;11(6):417-9. Epub 2011 Aug 10. PMID: 21831723.

Shechner T. Gender identity disorder: a literature review from a developmental perspective. *Isr J Psychiatry Relat Sci*. 2010;47(2):132-8. PMID: 20733256.

Shields J, Cohen R, Glassman J, Whitaker K, Franks H, Bertolini I. Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *J Adolesc Health*. 2013 Feb;52(2):248-50. Epub 2012 Aug 15. PMID: 23332492.

Simopoulos E, Khin Khin E. Fundamental principles inherent in the comprehensive care of transgender inmates. *J Am Acad Psychiatry Law*. 2014;42(1):26-36. PMID: 24618516.

Slabbekoorn D, van Goozen SH, Sanders G, Gooren LJ, Cohen-Kettenis PT. The dermatoglyphic characteristics of transsexuals: is there evidence for an organizing effect of sex hormones. *Psychoneuroendocrinology*. 2000 May;25(4):365-75. PMID: 10725613.

Slabbekoorn D., Van Goozen S., Gooren L., Cohen-Kettenis P. Effects of Cross-Sex Hormone Treatment on Emotionality in Transsexuals. *IJT*. 2001 Jul-Sept; 5(3):20 pages.http://www.symposion.com/ijt/ijtvo05no03_02.htm.

Slaby RG, Frey KS. Development of gender constancy and selective attention to same-sex models. *Child Dev*. 1975 Dec;46(4):849-56. PMID: 1201664.

Smilkstein G. The family APGAR: a proposal for a family function test and its use by physicians. *J Fam Pract*. 1978 Jun;6(6):1231-9. PMID: 660126.

Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry.* 2001 Apr;40(4):472-81. PMID: 11314574.

A-Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med.* 2005 Jan;35(1):89-99. PMID: 15842032.

B-Smith Y, van Goozen S, Kuiper A, Cohen-Kettenis P. Transsexual subtypes: clinical and theoretical significance. *Psychiatry Res.* 2005 Dec 15;137(3):151-60. Epub 2005 Nov 17. PMID: 16298429.

A-Sørensen T. A follow-up study of operated transsexual males. *Acta Psychiatr Scand.* 1981 May;63 (5):486-503. PMID: 7315491.

B-Sørensen T. A follow-up study of operated transsexual females. *Acta Psychiatr Scand.* 1981 Jul;64 (1):50-64. PMID: 7315494.

Sørensen T, Hertoft P. Male and female transsexualism: the Danish experience with 37 patients. *Arch Sex Behav* 1982 Apr;11(2):133-55. PMID: 7125885.

Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry.* 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

Stieglitz KA. Development, risk, and resilience of transgender youth. *J Assoc Nurses AIDS Care.* 2010 May-Jun;21(3):192-206Epub 2010 Mar 29. PMID: 20347346.

Stephens SC, Bernstein KT, Philip SS. Male to female and female to male transgender persons have different sexual risk behaviors yet similar rates of STDs and HIV. *AIDS Behav*. 2011 Apr;15(3):683-6. PMID: 20694509.

Stinson B. A study of twelve applicants for transsexual surgery. *Ohio State Med J*. 1972 Mar;68 (3):245-9. PMID: 4401539.

Stojanovic B, Djordjevic ML. Anatomy of the clitoris and its impact on neophalloplasty (metoidioplasty) in female transgenders. *Clin Anat*. 2015 Apr;28(3):368-75. Epub 2015 Mar 4. PMID: 25740576.

Strauss B, Richter-Appelt H (1995) *Fragebogen zur Beurteilung des eigenen Körpers (FBek), Handanweisung*. Hogrefe, Göttingen Bern Toronto Seattle.

Stroumsa D. The state of transgender health care: policy, law, and medical frameworks. *Am J Public Health* . 2014 Mar;104(3):e31-8. Epub 2014 Jan 16. PMID: 24432926.

Sultan B. Transsexual prisoners: how much treatment is enough? *New Engl Law Rev*. 2003 Summer;37(4):1195-230. PMID: 15295855.

Sundbom E, Bodlund O. Prediction of outcome in transsexualism by means of the Defense Mechanism Test and multivariate modeling: a pilot study. *Percept Mot Skills*. 1999 Feb;88(1):3-20. PMID: 10214627.

Swaab DF. Sexual differentiation of the human brain: relevance for gender identity, transsexualism and sexual orientation. *Gynecol Endocrinol*. 2004 Dec;19(6):301-12. PMID: 15724806.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Suicidal ideation among patients with gender identity disorder. *Psychiatry Res.* 2011 Nov 30;190(1):159-62. Epub 2011 May 25. PMID: 21612827.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Factors predicting psychiatric co-morbidity in gender-dysphoric adults. *Psychiatry Res.* 2012 Dec 30;200(2-3):469-74. Epub 2012 Aug 9. PMID: 22884214.

Titus-Ernstoff L, Perez K, Hatch EE, Troisi R, Palmer JR, Hartge P, Hyer M, Kaufman R, Adam E, Strohsnitter W, Noller K, Pickett KE, Hoover R. Psychosexual characteristics of men and women exposed prenatally to diethylstilbestrol. *Epidemiology.* 2003 Mar;14(2):155-60. PMID: 12606880.

Torres A, Gómez-Gil E, Vidal A, Puig O, Boget T, Salamero M. Gender differences in cognitive functions and influence of sex hormones. *Actas Esp Psiquiatr.* 2006 Nov-Dec;34(6):408-15. Spanish. PMID: 17117339.

Tourbach SA, Hunter-Smith D, Morrison WA. Long anterior urethral reconstruction using a jejunal free flap. *J Plast Surg Hand Surg.* 2011 Feb;45(1):54-6. PMID: 21446801.

Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: lessons from female- to-male transsexuals (FMT) treated with pharmacological testosterone therapy. *J Sex Med.* 2010 Nov;7(11):3758-64. Epub 2010 Aug 16. PMID: 20722789.

Trentacosti AM. *Epoietin alpha: FDA overview of patient reported outcome (PRO) claims.* 2007. www.fda.gov/ohrms/dockets/ac/07/slides/2007-4315s1-09-FDA-Trentacosti.ppt.

Trum H, Hoebeke P, Gooren L. Sex reassignment of transsexual people from a gynecologist's and urologist's perspective. *Acta Obstet Gynecol Scand.* 2015 Jun;94(6):563-7. Epub 2015 Mar 29. PMID: 25721104.

Case 7:16-cv-00108-Q Document 26 Filed 10/21/16 Page 878 of 919 PageID 1344
T'Sjoen G, Weyers S, Taes Y, Lapaauw S, Roeyt, Goemaere S, Kaufman. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. *J Clin Densitom.* 2009 Jul-Sep;12(3):306-13. Epub 2009 Jan 3. PMID: 19121966.

T'Sjoen G, De Cuypere G, Monstrey S, Hoebeke P, Freedman F, Appari M, Holterhus P, Van Borsel J, Cools M. Male gender identity in complete androgen insensitivity syndrome. *Arch Sex Behav.* 2011 Jun;40(3):635-8. Epub 2010 Apr 1. PMID: 20358272.

TSjoen G, Van Caenegem E, Wierckx K. Transgenderism and reproduction. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):575-9. PMID: 24468761.

Tsoi WF, Kok LP, Long FY. Male transsexualism in Singapore: a description of 56 cases. *Br J Psychiatry.* 1977 Oct;131:405-9. PMID: 922268.

Tsoi WF. The prevalence of transsexualism in Singapore. *Acta Psychiatr Scand.* 1988 Oct;78 (4):501-4. PMID: 3265846.

Tsoi WF. Male and female transsexuals: a comparison. *Singapore Med J.* 1992 Apr;33(2):182-5. PMID: 1621125.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J.* 1993 Dec;34(6):515-7. PMID: 8153713.

Tsoi WF, Kok LP, Yeo KL, Ratnam SS. Follow-up study of female transsexuals. *Ann Acad Med Singapore.* 1995 Sep;24(5):664-7. PMID: 8579306.

Tsushima WT, Wedding D. MMPI results of male candidates for transsexual surgery. *J Pers Assess.* 1979. Aug;43(4):385-7. PMID: 383946.

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. *Sexual and Relationship Therapy*. 2008 May; 23(2):141-5. (Not in PubMed)

Urban R, Teng N, Kapp D. Gynecologic malignancies in female-to-male transgender patients: the need of original gender surveillance. *Am J Obstet Gynecol*. 2011 May;204(5):e9-e12. Epub 2011 Feb 26. PMID: 21354550.

Vacchiano RB, Strauss PS. The construct validity of the Tennessee self concept scale. *J Clin Psychol*. 1968 Jul;24(3):323-6. PMID: 5661752.

Van Caenegem E, Wierckx K, Taes Y, Dedeker D, Van de Peer F, Toye K, Kaufman J, T'Sjoen G. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab*. 2012 Jul;97(7):2503-11. Epub 2012 May 7. PMID: 22564669.

A-Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman J, Schreiner T, Haraldsen I. T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone*. 2013 May;54(1):92-7. Epub 2013 Jan 28. PMID: 23369987.

B-Van Caenegem E, Verhaeghe E, Taes Y, Wierckx K, Toye K, Goemaere S, Zmierzak H, Hoebeke P, Monstrey S, T'Sjoen G. Long-term evaluation of donor-site morbidity after radial forearm flap phalloplasty for transsexual men. *J Sex Med*. 2013 Jun;10(6):1644-51. Epub 2013 Mar 27. PMID: 23534878.

Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman J, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol*. 2015 Feb;172(2):163-71. PMID: 25550352.

Van Caenegem E, Wierckx K, Elaut E, Buysse A, Dewaele A, Van Nieuwerburgh F, De Cuypere G, T'Sjoen G. Prevalence of Gender Nonconformity in Flanders, Belgium. *Arch Sex Behav*. 2015 Jul;44 (5):1281-7. Epub 2015 Jan 15. PMID: 25588709.

VanderLaan DP, Vokey JR, Vasey PL. Is Transgendered Male Androphilia Familial in Non-Western Populations? The Case of a Samoan Village. *Arch Sex Behav*. 2013; 42:361–70. PMID: 23187702.

Van Kesteren PJ, Gooren LJ, Megens JA. An epidemiological and demographic study of transsexuals in The Netherlands. *Arch Sex Behav*. 1996 Dec;25(6):589-600. PMID: 8931882.

Van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997 Sep;47(3):337-42. PMID: 9373456.

Vasey PL, Bartlett NH. What can the Samoan "Fa'afafine" teach us about the Western concept of gender identity disorder in childhood? *Perspect Biol Med*. 2007 Autumn;50(4):481-90. PMID: 17951883.

Veatch RM. Indifference of subjects: An alternative to equipoise in randomized clinical trials. *Soc Phil Policy*. 2002; 19:295-323. PMID: 12678091.

Veale J. Prevalence of transsexualism among New Zealand passport holders. *Aust N Z J Psychiatry*. 2008 Oct;42(10):887-9. PMID: 18777233.

Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study. *J Adolesc Health*. 2015 Oct;57(4):367-73. Epub 2015 Jun 25. PMID: 26119518.

Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. *J Sex Med*. 2009 Apr;6(4):1018-23. Epub 2008 Mar 4. PMID: 18331254.

Vujović S, Popović S, Mrvošević Marojević L, Ivović M, Tančić-Gajić M, Stojanović M, Marina LV, Barać M, Barać B, Kovačević M, Duišin D, Barišić J, Djordjević ML, Micić D. Finger length ratios in Serbian transsexuals. *Scientific World Journal*. 2014 May 20;2014:Article 763563. 4 pages. PMID: 24982993.

Walinder J, Thuwe I. *A social-psychiatric follow-up study of 24 sex-reassigned transsexuals*. Gothenburg: Scandinavian University Books, Akademiforlaget. 1975.

Walinder J, Lundstrom B, Thuwe I. Prognostic factors in the assessment of male transsexuals for sex reassignment. *Br J Psychiatry*. 1978;132: 16-20. (Not in PubMed)

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992 Jun;30(6):473-83. PMID: 1593914.

Watson D, Friend R. Measurement of social-evaluative anxiety. *J Consult Clin Psychol*. 1969 Aug;33(4):448-57. PMID: 5810590.

Winter S, Diamond M, Green J, Karasic D, Reed T, Whittle S, Wylie K. Transgender people: health at the margins of society. *Lancet*. Epub 16 June 2016 [http://dx.doi.org/10.1016/S0140-6736\(16\)00683-8](http://dx.doi.org/10.1016/S0140-6736(16)00683-8)

Weigert R, Frison E, Sessieq Q, Al Mutairi K, Casoli V. Patient satisfaction with breasts and psychosocial, sexual, and physical well-being after breast augmentation in male-to-female transsexuals. *Plast Reconstr Surg*. 2013 Dec;132(6):1421-9. PMID: 24281571.

A-Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med*. 2009 Mar;6(3):752-60. Epub 2008 Nov 17. PMID: 19040622.

B-Weyers S, Decaestecker K, Verstraelen H, Monstrey S, T'Sjoen G, Gerris J, Hoebeke P, Villeirs G. Clinical and transvaginal sonographic evaluation of the prostate in transsexual women. *Urology*. 2009 Jul;74(1):191-6. Epub 2009 Apr 23. PMID: 19395005.

WHO 1996: Harper A. Manual for World Health Organization Quality of Life Abbreviated. Director Dr. J. Orley. http://www.who.int/mental_health/media/en/76.pdf.

WHO 2011: Carlos F. Caceres CF, GerbaseA, Ying-Ru Lo Y-R, Rodolph M (key drafters). *Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with other men and transgender people. Recommendations for a public health approach*. World Health Organization. 2011. http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/.

WHO 2014: Chris Beyrer C, Kamarulzaman A (co-chairs.) World Health Organization. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations*. July 2014. www.who.int/hiv/pub/guidelines/keypopulations/en/.

WHO 2015: Poteat T, Keatley J. (key drafters). *Policy Brief: Transgender People and HIV*. World Health Organization. July 2015. <http://www.who.int/hiv/pub/transgender/transgender-hiv-policy/en/>.

Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther*. 2005 Jan-Feb;31(1):1-20. PMID: 15841702.

A-Wierckx K, Elaut E, Van Caenegem E, Van De Peer F, Dedeker D, Van Houdenhove E, T'Sjoen G. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur J Endocrinol*. 2011 Aug;165(2):331-7. Epub 2011 May 20. PMID: 21602316.

B-Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011 Dec;8(12):3379-88. Epub 2011 Jun 23. PMID: 21699661.

Wylie K, Knudson G, Khan S, Bonierbale M, Watanyusakul S, Baral S. Serving transgender people: clinical care considerations and service delivery models in transgender health. *Lancet*. Epub 16 June 2016. [http://dx.doi.org/10.1016/S0140-6736\(16\)00682-6](http://dx.doi.org/10.1016/S0140-6736(16)00682-6)

A-Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedeker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. *Hum Reprod*. 2012 Feb;27(2):483-7. Epub 2011 Nov 28. PMID: 22128292.

Case 7:16-cv-00108-0 Document 26 Filed 10/21/16 Page 883 of 919 PageID 1349
B-Wierckx K, Muelier S, Weyers S, Van Cuyper E, Ruel G, Heylens G, T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. *J Sex Med.* 2012 Oct;9(10):2641- 51. Epub 2012 Aug 20. PMID: 22906135.

C-Wierckx K, Stuyver I, Weyers S, Hamada A, Agarwal A, De Sutter P, T'Sjoen G. Sperm freezing in transsexual women. *Arch Sex Behav.* 2012 Oct;41(5):1069-71. PMID: 22968492.

Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, Kaufman J, T'Sjoen G. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol.* 2013 Oct;169(4):471-8. Epub 2013 Sep 13. PMID: 23904280.

A-Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med.* 2014 Jan;11(1):107-18. Epub 2013 Oct 24. PMID: 24165564.

B-Wierckx K, Gooren L, T'Sjoen G. Clinical review: Breast development in trans women receiving cross-sex hormones. *J Sex Med.* 2014 May;11(5):1240-7. Epub 2014 Mar 12. PMID: 24618412.

Williamson C. Providing care to transgender persons: a clinical approach to primary care, hormones, and HIV management. *J Assoc Nurses AIDS Care.* 2010 May-Jun;21(3):221-9. Epub 2010 Apr 3. PMID: 20363651.

Wilson CA, Davies DC. The control of sexual differentiation of the reproductive system and brain. *Reproduction.* 2007 Feb;133(2):331-59. PMID: 17307903.

Wilson EC, Garofalo R, Harris DR, Belzer M. Sexual risk taking among transgender male-to-female youths with different partner types. *Am J Public Health.* 2010 Aug;100(8):1500-5. Epub 2009 Nov 12. PMID: 20622176.

Wilson E, Pant SB, Comfort M, Ekstrand M. Stigma and HIV risk among Metis in Nepal. *Cult Health Sex.* 2011 Mar;13(3):253-66. PMID: 21058085.

Wilson P, Sharp C, Carr S. The prevalence of gender dysphoria in Scotland: a primary care study. *Brit J Gen Pract.* 1999; 49 (449): 991-2. PMID: 10824346.

Wilson RC, Nimkarn S, Dumic M, Obeid J, Azar MR, Najmabadi H, Saffari F, New MI. Ethnic- specific distribution of mutations in 716 patients with congenital adrenal hyperplasia owing to 21- hydroxylase deficiency. *Mol Genet Metab.* 2007 Apr;90(4):414-21. Epub 2007 Feb 1. Erratum in: *Mol Genet Metab.* 2008 Feb;93(2):219. Azar, Maryam [corrected to Azar, Maryam Razzaghy]. PMID: 17275379.

A-Wise LA, Palmer JR, Hatch EE, Troisi R, Titus-Ernstoff L, Herbst AL, Kaufman R, Noller KL, Hoover RN. Secondary sex ratio among women exposed to diethylstilbestrol in utero. *Environ Health Perspect.* 2007 Sep;115(9):1314-9. PMID: 17805421.

B-Wise LA, Titus-Ernstoff L, Palmer JR, Hoover RN, Hatch EE, Perez KM, Strohsnitter WC, Kaufman R, Anderson D, Troisi R. Time to pregnancy and secondary sex ratio in men exposed prenatally to diethylstilbestrol. *Am J Epidemiol.* 2007 Oct 1;166(7):765-74. Epub 2007 Jun 27. PMID: 17596265.

Wise TN, Meyer JK. The border area between transvestism and gender dysphoria: transvestitic applicants for sex reassignment. *Arch Sex Behav.* 1980 Aug;9(4):327-42. PMID: 7416946.

Wolfradt U, Engelmann S. Depersonalization, fantasies, and coping behavior in clinical context. *J Clin Psychol.* 1999 Feb;55(2):225-32. PMID: 10100823.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. *Arch Sex Behav.* 2001 Jun;30(3):301-10 PMID: 11330119.

WPATH 2001 Meyer III W, Bockting WO, Cohen-Kettenis P, Coleman E, DiCeglie D, Devor H, Gooren L, Hage JJ, Kirk S, Kuiper B., Laub D., Lawrence A., Menard Y., Monstrey S, Patton J, Schaefer L., Webb A, Wheeler CC .*The Harry Benjamin International Gender Dysphoria Association's Standards Of Care For Gender Identity Disorders.* (6th version) February, 2001.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=4655.

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WPATH 2012 Coleman E, Bouling W, Botzer M, Cohen-Kettenis P, DeCuypere G, Erdman J, Fasser E, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Istar Lev A, Mayer G, Meyer-Bahlburg H, Paxton Hall B, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. *Standards of care for the health of transsexual, transgender, and gender-nonconforming people*. (7th version) 2012. http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926.

Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):570-4. PMID: 24468760.

Wyler J, Battegay R, Krupp S, Rist M, Rauchfleisch U. [Transsexualism and its therapy]. *Schweiz Arch Neurol Neurochir Psychiatr*. 1979;124(1):43-58. PMID: 482895.

Yahyaoui R, Esteva I, Haro-Mora J, Almaraz M, Morcillo S, Rojo-Martínez G, Martínez J, Gómez- Zumaquero J, González I, Hernando V, Soriguer F. Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab*. 2008 Jun;93(6):2230-3. Epub 2008 Mar 18. PMID: 18349066.

Yik Koon, T. (2002). *The Mak Nyahs: Malaysian Male to Female Transsexuals*. (Chapter 4) Eastern Universities Press.

Zhu, Y, Imperato-McGinley, J, Male Sexual Differentiation Disorder and 5 α -Reductase-2 Deficiency. *Glob. libr. women's med.*, (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10350. (Not in PubMed.)

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983 Jun;67(6):361-70. PMID: 6880820.

Zimmermann A, Zimmer R, Kovacs L, Einödshofer S, Herschbach P, Henrich G, Tunner W, Biemer E, Papadopoulos N. [Transsexuals' life satisfaction after gender transformation operations]. *Chirurg*. 2006 May;77(5):432-8. German. Erratum in *Chirurg*. 2006 Jun;77(6):530. PMID: 16437228.

Zoni AC, González MA, Sjögren HW. Syphilis in the most at-risk populations in Latin America and the Caribbean. *Am J Trop Med Hyg*. 2011 Jun;82(6):1033-40. PMID: 21551111.

Zucker KJ, Bradley SJ, Hughes HE. Gender dysphoria in a child with true hermaphroditism. *Can J Psychiatry*. 1987 Oct;32(7):602-9. PMID: 3676994.

A-Zucker KJ, Bradley SJ, Kuksis M, Pecore K, Birkenfeld-Adams A, Doering RW, Mitchell JN, Wild J. Gender constancy judgments in children with gender identity disorder: evidence for a developmental lag. *Arch Sex Behav*. 1999 Dec;28(6):475-502. PMID: 10650437.

B-Zucker KJ. Intersexuality and gender identity differentiation. *Annu Rev Sex Res*. 1999;10:1-69. PMID: 10895247.

Zucker K, Cohen-Kettenis P, Drescher J, Meyer-Bahlburg H, Pfäfflin F, Womack W. Memo outlining evidence for change for gender identity disorder in the DSM-5. *Arch Sex Behav*. 2013 Jul;42(5):901-14. PMID: 23868018.

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HEALTH AFFAIRS

THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

JUL 29 2016

MEMORANDUM FOR ASSISTANT SECRETARY OF THE ARMY (MANPOWER AND
RESERVE AFFAIRS)
ASSISTANT SECRETARY OF THE NAVY (MANPOWER AND
RESERVE AFFAIRS)
ASSISTANT SECRETARY OF THE AIR FORCE (MANPOWER
AND RESERVE AFFAIRS)
DIRECTOR, DEFENSE HEALTH AGENCY
DIRECTOR, HEALTH, SAFETY AND WORK LIFE, U.S. COAST
GUARD

SUBJECT: Guidance for Treatment of Gender Dysphoria for Active and Reserve
Component Service Members

In accordance with Department of Defense Instruction (DoDI) 1300.28, "In-Service Transition for Transgender Service Members," June 30, 2016, and Directive-Type Memorandum (DTM)16-005, "Military Service of Transgender Service Members," June 30, 2016, this memorandum provides guidance for the medical care of transgender Service members. This memorandum supplements requirements in those issuances; it does not supersede any such requirements.

General Provisions:

The Military Health System (MHS) will either provide or arrange consultation for medically necessary care for members on active duty for a period of more than 30 days (referred to as Active Duty Service members (ADSMs) throughout the remainder of this document). Such care is based upon the individual's unique health care needs and, following initial evaluation, may include counseling and behavioral health services, medical support, and assistance with establishing a treatment plan for the Service member's submission to the unit commander, followed by any medically necessary treatment.

Until the DoD is able to promulgate specific clinical practice guidelines for the care of transgender personnel, the MHS will adhere to the attached 2009 version of the Endocrine Society's Standards of Care, "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," as the primary guideline to provide consistent, evidence based care to transitioning patients. Explanation of any clinically indicated deviation from the guideline should be documented in the patient's health record. Clinical Practice Guidelines from other professional societies may also help inform clinical decision making (e.g., the 2015 American Psychological Association Guidelines for Psychological Practice with Transgender and Gender Nonconforming People and the World Professional Association for Transgender Health Standards of Care). Key components of medical care for the purpose of treating gender dysphoria include initial assessment and, based upon that assessment of the individual's needs,

the establishment of a treatment plan which may include real life experience (RLE) that is provided in a manner consistent with the requirements of DoDI 1300.28 and DTM 16-005 regarding RLE, cross-sex hormone therapy, and surgical transition. Treatment plans must be individualized and approved by a military medical provider. The following guidance addresses various stages of treatment:

1. For Active Duty Service members (ADSMs) seeking initial treatment for gender dysphoria, a diagnosis of gender dysphoria must be established by a privileged behavioral health provider (or similarly qualified civilian provider if unavailable in a military facility), with appropriate referral to other types of providers as indicated or required. The assessment should be comprehensive in nature, including exclusion of other causes for dysphoria, and lead to formulation of an initial treatment plan.
2. For ADSMs who have already received a diagnosis of gender dysphoria and established a treatment plan approved by a military medical provider, and who desire to proceed to or continue cross-sex hormone therapy, an endocrinologist or other physician with appropriate professional expertise should exclude medical conditions making hormone therapy unsafe, may initiate or continue hormone therapy if indicated as medically necessary, and monitor response to hormones in accordance with the Endocrine Society's Standards of Care guidelines, to include periodic screening for hormone associated adverse outcomes.
3. ADSMs with an established treatment plan desiring surgical treatment following a period of RLE and who are compliant with all facets of an approved treatment plan should be referred to an appropriately qualified surgeon for evaluation. The surgeon should fully discuss all surgical options and potential complications in order to provide informed consent before surgery is proposed. Consistent with current DoD policies, purely cosmetic or other non-medically necessary surgery is not authorized.
4. Any Service member for whom the Defense Enrollment Eligibility Reporting System has recorded a gender change, or who is in the process of obtaining such a change, must have an ongoing plan to address needed medical care, including follow up of hormone treatment and any appropriate health screening.
5. Unless and until adequate surgical capabilities have been established in DoD Military Treatment Facilities (MTFs), medically necessary surgical treatment will be evaluated using the existing MHS waiver process for private sector care for Active Duty members under the Supplemental Health Care Program (SHCP). This standardized process requires referral through the Service chain of command and review and approval by the Director, Defense Health Agency (DHA).
6. The expectation is for the MHS to provide an interdisciplinary team approach to transition care in accordance with evidence based guidelines and practices, reinforcing at all times the transgender Service member's right to receive all medical care with dignity and respect. Provision of care may involve multiple facilities and require appropriate care coordination between providers. In no circumstance will a provider be required to

deliver care that he or she feels unprepared to provide either by lack of clinical skill or due to ethical, moral or religious beliefs. However, referral to an appropriate provider or level of care is required under such circumstances.

7. As with all other medical conditions, in the first 180 days of service in the military, all personnel must continue to meet the medical standards associated with accession (DoDI 6130.03, "Medical Standards for Appointment, Enlistment, or Induction in the Military Services"). Ongoing fitness for duty and deployment screening after 180 days shall be assessed in accordance with current Service practices and policies applied to other medical conditions.

Central Coordination:

1. Service Central Coordination Cells (SCCC) established under DoDI 1300.28 shall provide multi-disciplinary (e.g., medical, legal, military personnel management) expert advice and assistance to commanders with regard to service by transgender Service members and gender transition in the military to assist commanders in the execution of DoD, Military Department, and Service policies and procedures.
2. The Under Secretary of Defense for Personnel and Readiness (USD(P&R)) has established a Central Coordination Cell with Office of the Secretary of Defense, DHA, and Service representatives to oversee consistent and uniform implementation of DoDI 1300.28, provide consultation to SCCC's, and receive and analyze data reported by the Services. The Central Coordination Cell is not a substitute for SCCC's, but provides information and advice on policy matters, and assistance with identification and coordination of needed treatment resources, when necessary. DHA has provided a senior representative to facilitate coordination of care and services delivered by the managed care support contractors and the DHA Waiver Authority process.
3. To assist Commanders and Service members until each Service establishes its own SCCC, the DoD Central Coordination Cell has established the following website: <https://prext.osd.mil/DoDCCC>. This is a Common Access Card-enabled website for secure questions by all Service members. Policy documents and Frequently Asked Questions reside on this website and questions will be answered by policy, legal and medical experts.

Service and DHA Requirements and Responsibilities:

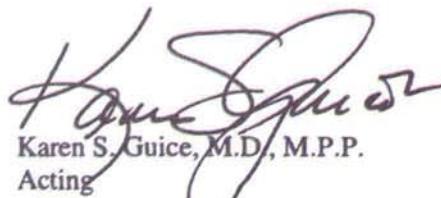
1. Each Service and DHA shall develop and submit an assessment of current Service medical capacity and expertise in providing medical and surgical support for treating gender dysphoria to the USD(P&R) no later than August 31, 2016. This assessment should include a listing of MTFs at which interdisciplinary care and treatment are available or under development for this purpose, and use the attached data reporting template.

2. Each Service and DHA shall develop an education and training plan for both privileged and non-privileged medical personnel no later than November 1, 2016. This plan should detail how the Service will ensure familiarity with applicable Department policies and requirements, evidence-based practice guidelines and standards of care, and any Service-specific policies. To the extent practicable, training plans and requirements, and additional procedural guidance for care and services will be consistent across the MHS, and will be published as DHA procedural guidance.
3. Each Service and DHA shall be prepared to begin supporting transition medical care to transgender ADSMs no later than October 1, 2016. At a minimum, Services will be expected to provide, by referral if necessary, initial assessment, psychological and pharmaceutical support. As directed by the Secretary of Defense, in the period prior to October 1, 2016, the Military Departments and Services will address requests for gender transition from serving transgender Service members on a case-by-case basis, following the spirit and intent of DTM 16-005 and DoDI 1300.28. Until the capability of MHS MTFs to provide surgical transition services has been documented, any proposed genital surgical transition procedures within MTFs shall be prospectively reviewed by the appropriate Surgeon General or, in the case of the National Capital Region facilities, the Director, DHA. Approvals will be reported to the Assistant Secretary of Defense for Health Affairs (ASD(HA)) monthly.
4. The Director, DHA, will ensure that the Managed Care Support Contractors identify appropriate referral resources with providers experienced in care and treatment of transgender persons to ensure availability of care to complement MTF capabilities. An inventory of such resources shall be provided to the ASD(HA) not later than August 31, 2016.
5. The Director, DHA, will evaluate proposed referrals to the TRICARE network for surgical treatment in accordance with the Supplemental Health Care Program (SHCP). MHS care for ADSMs from non-DoD providers is governed by section 1074(c)(2) of title 10, U.S. Code, and section 199.16 of title 32, Code of Federal Regulations. Under these provisions, the SHCP normally follows TRICARE rules, which disallow surgical treatment of gender dysphoria, but the prohibition is subject to waiver for medically necessary care for ADSMs. The Director, DHA, is authorized to grant waivers on a case-by-case basis. Waiver requests will follow existing processes. Each waiver request, with appropriate clinical documentation, should be submitted through the Surgeon General concerned, to the Director, DHA.
6. To the extent a SHCP waiver would be needed to authorize non-surgical care for an ADSM, this memorandum approves such a waiver on a blanket basis if such care is recommended by a military health care provider in accordance with established SHCP procedures and this memorandum.

7. With respect to Reserve Component Service members not on active duty for a period of more than 30 days who initiate or are involved in a gender transition process, the Services shall establish procedures to ensure that a medical diagnosis and treatment plan (or significant revisions to a treatment plan) or a recommendation for a change in a member's gender marker made by a civilian medical provider is reviewed and approved by an appropriate military medical provider and communicated in a timely and efficient manner with the Reserve Component command involved.

ASD(HA) Responsibilities:

1. The ASD(HA) shall establish collaboration with the Veterans Health Administration and academic medical centers to support Service training plans and specialty consultations, including via telemedicine, where necessary and appropriate.
2. The ASD(HA) shall monitor compliance with this memorandum, which may include assessing Service and DHA performance on all provisions contained within this memorandum.



Karen S. Guice, M.D., M.P.P.
Acting

Attachments:

As stated

cc:

Under Secretary of Defense for Personnel and Readiness
Assistant Secretary of Defense (Manpower and Reserve Affairs)
Surgeon General of the Army
Surgeon General of the Navy
Surgeon General of the Air Force
Joint Staff Surgeon
Medical Office of the Marine Corps

**Department of Health and Human Services
DEPARTMENTAL APPEALS BOARD
Appellate Division**

NCD 140.3, Transsexual Surgery
Docket No. A-13-87
Decision No. 2576
May 30, 2014

DECISION

The Board has determined that the National Coverage Determination (NCD) denying Medicare coverage of all transsexual surgery as a treatment for transsexualism is not valid under the “reasonableness standard” the Board applies. The NCD was based on information compiled in 1981. The record developed before the Board in response to a complaint filed by the aggrieved party (AP), a Medicare beneficiary denied coverage, shows that even assuming the NCD’s exclusion of coverage at the time the NCD was adopted was reasonable, that coverage exclusion is no longer reasonable. This record includes expert medical testimony and studies published in the years after publication of the NCD. The Centers for Medicare & Medicaid Services (CMS), which is responsible for issuing and revising NCDs, did not defend the NCD or the NCD record in this proceeding and did not challenge any of the new evidence submitted to the Board.

Effect of this decision

Since the NCD is no longer valid, its provisions are no longer a valid basis for denying claims for Medicare coverage of transsexual surgery, and local coverage determinations (LCDs) used to adjudicate such claims may not rely on the provisions of the NCD. The decision does not bar CMS or its contractors from denying individual claims for payment for transsexual surgery for other reasons permitted by law. Nor does the decision address treatments for transsexualism other than transsexual surgery. The decision does not require CMS to revise the NCD or issue a new NCD, although CMS, of course, may choose to do so. CMS may not reinstate the invalidated NCD unless it has a different basis than that evaluated by the Board. 42 C.F.R. § 426.563.

CMS must implement this Board decision within 30 days and apply any resulting policy changes to claims or service requests made by Medicare beneficiaries other than the AP for any dates of service after that implementation. With respect to the AP’s claim in

particular, CMS and its contractors must “adjudicate the claim without using the provision(s) of the NCD that the Board found invalid.” 42 C.F.R. § 426.560(b)(1).¹

Legal background

With exceptions not relevant here, section 1862(a)(1)(A) of the Social Security Act (Act) (42 U.S.C. § 1395y(a)(1)(A)) bars Medicare payment for items or services “not reasonable and necessary for the diagnosis or treatment of illness or injury[.]”² CMS refers to this requirement as the “medical necessity provision.” 67 Fed. Reg. 54,534, 54,536 (Aug. 22, 2002). An NCD is “a determination by the Secretary [of Health and Human Services] with respect to whether or not a particular item or service is covered nationally under [title XVIII (Medicare)].” Act §§ 1862(l)(6)(A), 1869(f)(1)(B); *see also* 42 C.F.R. § 400.202 (NCD “means a decision that CMS makes regarding whether to cover a particular service nationally under title XVIII of the Act.”). NCDs “describe the clinical circumstances and settings under which particular [Medicare items and] services are reasonable and necessary (or are not reasonable and necessary).” 67 Fed. Reg. at 54,535. When CMS issues NCDs, they apply nationally and are binding at all levels of administrative review of Medicare claims. 42 C.F.R. § 405.1060. CMS and its contractors use applicable NCDs in determining whether a beneficiary may receive Medicare reimbursement for a particular item or service. 42 C.F.R. §§ 405.920, 405.921.

A Medicare beneficiary “in need of coverage for a service that is denied based on ... an NCD” is an “aggrieved party” who may challenge the NCD by filing a “complaint” with the Board.³ Act § 1869(f)(1); 42 C.F.R. §§ 426.110, 426.320. The complaint must comply with the requirements for a valid complaint in 42 C.F.R. § 426.500 in order to be accepted by the Board. 42 C.F.R. §§ 426.510(b)(2), 426.505(c)(2). After the Board notifies CMS of the receipt of a complaint that is acceptable under the regulations, CMS produces the “NCD record,” which “consists of any document or material that CMS

¹ *See generally* 42 C.F.R. § 426.560(b) (setting out the effects of a Board NCD decision); 42 C.F.R. § 426.555 (specifying what the Board’s decision “may not do”). This decision has no effects beyond those set out in 42 C.F.R. § 426.560(b) and does not impose on CMS or its contractors any orders or requirements prohibited by 42 C.F.R. § 426.555.

² The table of contents to the current version of the Social Security Act, with references to the corresponding United States Code chapter and sections, can be found at http://www.socialsecurity.gov/OP_Home/ssact/ssact-toc.htm.

³ The regulations also provide that a person other than the aggrieved party with an interest in the issues may petition to participate in the review process as an *amicus curiae*. 42 C.F.R. §§ 426.510(f), 426.513. The Board posts on its website notice of the NCD complaint specifying a time period for requests to participate in the review. 42 C.F.R. § 426.510(f).

considered during the development of the NCD” including “medical evidence considered on or before the date the NCD was issued” 42 C.F.R. §§ 426.510(d)(3), 426.515, 426.518(a). The aggrieved party submits a statement “explaining why the NCD record is not complete, or not adequate to support the validity of the NCD under the reasonableness standard,” and CMS may submit a response “in order to defend the NCD.” 42 C.F.R. § 426.525(a), (b). If the Board determines that the NCD record “is complete and adequate to support the validity of the NCD,” the review process ends with the Board’s “[i]ssuance of a decision finding the record complete and adequate to support the validity of the NCD” 42 C.F.R. § 426.525(c)(1), (2). If the Board determines that the record is *not* complete and adequate to support the validity of the NCD, the Board “permits discovery and the taking of evidence . . . and evaluates the NCD” in accordance with the requirements of Part 426, including conducting a hearing, unless the matter can be decided on the written record. 42 C.F.R. §§ 426.525(c)(3), 426.531(a)(2).

Prior to issuing a decision, the Board must review any “new evidence” admitted to the record before the Board and determine whether it “has the potential to significantly affect” the Board’s evaluation. 42 C.F.R. §§ 426.340(a), (b), 426.505(d)(3). “New evidence” is defined as “clinical or scientific evidence that was not previously considered by . . . CMS before the . . . NCD was issued.” 42 C.F.R. § 426.110. If the Board so concludes, the Board stays proceedings for CMS “to examine the new evidence, and to decide whether [to] initiate[] . . . a reconsideration” of the NCD. 42 C.F.R. § 426.340(d). If CMS does not reconsider the NCD, or reconsiders it but does not change the challenged provision, the Board lifts the stay and the NCD challenge process continues. 42 C.F.R. § 426.340(f). At the end of that process, the Board closes the record and issues a decision that the challenged “provision of the NCD is valid” or “is not valid under the reasonableness standard.”⁴ 42 C.F.R. § 426.550. The Board’s decision “constitutes a final agency action and is subject to judicial review” on appeal by an aggrieved party. 42 C.F.R. § 426.566.

⁴ Section 426.547(b) states that the Board must make the decision available at the HHS Medicare Internet site and that “the posted decision does not include any information that identifies any individual, provider of service, or supplier.” CMS has indicated in the preamble to the Part 426 regulations that this provision was meant to protect the privacy of Medicare beneficiaries such as the AP. *See, e.g.*, 68 Fed. Reg. 63,692, 63,708 (Nov. 7, 2003) (“Board decisions regarding NCDs will be made available on the Medicare Internet site, without beneficiary identifying information”).

Case background

The NCD and the NCD record

The challenged NCD, titled “140.3, Transsexual Surgery,” states:⁵

Item/Service Description

Transsexual surgery, also known as sex reassignment surgery or intersex surgery, is the culmination of a series of procedures designed to change the anatomy of transsexuals to conform to their gender identity. Transsexuals are persons with an overwhelming desire to change anatomic sex because of their fixed conviction that they are members of the opposite sex. For the male-to-female, transsexual surgery entails castration, penectomy and vulva-vaginal construction. Surgery for the female-to-male transsexual consists of bilateral mastectomy, hysterectomy and salpingo-oophorectomy, which may be followed by phalloplasty and the insertion of testicular prostheses.

Indications and Limitations of Coverage

Transsexual surgery for sex reassignment of transsexuals is controversial. Because of the lack of well controlled, long-term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism, the treatment is considered experimental. Moreover, there is a high rate of serious complications for these surgical procedures. For these reasons, transsexual surgery is not covered.

NCD Record at 93. CMS’s predecessor, the Health Care Financing Administration (HCFA), published the NCD in the Federal Register on August 21, 1989.⁶ 54 Fed. Reg. 34,555, 34,572 (Aug. 21, 1989); NCD Record at 76, 78, 93, 128. The NCD quotes or paraphrases portions of an 11-page report that the former National Center for Health Care Technology (NCHCT) of the HHS Public Health Service (PHS) issued in 1981, titled

⁵ NCDs are available at http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?list_type=ncd.

⁶ The Federal Register notice stated, “This notice lists those current Medicare national coverage decisions which have been issued in the Medicare Coverage Issues Manual (HCFA Pub. 6).” 54 Fed. Reg. at 34,555.

“Evaluation of Transsexual Surgery” (1981 report).⁷ NCD Record at 13-23. The NCHCT forwarded the 1981 report to HCFA with a May 6, 1981 memorandum stating that the 1981 report “concludes that transsexual surgery should be considered experimental because of the lack of proven safety and efficacy of the procedures for the treatment of transsexualism” and recommending “that transsexual surgery not be covered by Medicare at this time.” *Id.* at 12.

The NCD record includes three April 1982 letters from the American Civil Liberties Union (ACLU) of Southern California disagreeing with HCFA’s noncoverage determination. *Id.* at 24-25, 26, 41-42. The ACLU submitted letters and affidavits from physicians and therapists supporting the medical necessity of transsexual surgery and taking issue with the non-coverage determination. *Id.* at 27-75. On May 11, 1982, the HCFA physicians panel, by a vote of five to two, recommended against referring the ACLU’s submissions to PHS, “on the basis that it does not contain information about new clinical studies or other medical and scientific evidence sufficiently substantive to justify reopening the previous PHS assessment.” *Id.* at 7, 9. Thus, although the NCD was issued in 1989, it was based on the analysis of medical and scientific publications in the 1981 report.

The NCD complaint

The AP in this case, a Medicare beneficiary whose insurer denied a physician’s order for sex reassignment surgery (transsexual surgery), filed an acceptable NCD complaint and supporting materials. CMS submitted the NCD record on May 15, 2013, and the AP submitted a statement of why the NCD record is not complete or adequate to support the validity of the NCD under the reasonableness standard (AP Statement) on June 14, 2013. The Board granted unopposed requests by six advocacy organizations to participate as amici curiae in the NCD review by filing written briefs arguing that the NCD was invalid. (Four of the amici submitted a joint brief.)⁸

⁷ The concluding summary of the 1981 NCHTC report stated in relevant part:

Transsexual surgery for sex reassignment of transsexuals is controversial. There is a lack of well controlled, long-term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism. There is evidence of a high rate of serious complications of these surgical procedures. The safety and effectiveness of transsexual surgery as a treatment of transsexualism is not proven and is questioned. Therefore, transsexual surgery must be considered still experimental.

NCD Record at 19.

⁸ The six amici are the Human Rights Campaign (HRC) and the World Professional Association for Transgender Health (WPATH), which each submitted briefs, and the FORGE Transgender Aging Network, the National Center for Transgender Equality, the Sylvia Rivera Law Project, and the Transgender Law Center, which submitted a joint brief.

On June 26, 2013, CMS notified the Board that it “declines to submit a response” to the AP’s statement. On December 2, 2013, the Board ruled that the NCD record “is not complete and adequate to support the validity of the NCD[.]” *NCD 140.3, Transsexual Surgery*, NCD Ruling No. 2 (Dec. 2, 2013) (NCD Ruling).⁹ The parties then jointly reported that they did not intend to submit additional evidence (except for curricula vitae (CVs) of the AP’s witnesses) or cross-examine any witness and asked the Board to close the NCD review record to the taking of evidence and decide the case based on the written record.

The Board determined that the new evidence in the record had the potential to significantly affect its review of the NCD and, as required, stayed proceedings for 10 days for CMS to examine the new evidence and decide whether to reconsider the NCD.¹⁰ *Order Closing Record & Staying Proceedings for CMS to Determine Whether to Reconsider NCD* (Feb. 25, 2014) (Order); 42 C.F.R. §§ 426.340(d), 426.505(d)(3). Two days later, CMS informed the Board by email that it “does not wish to reconsider the NCD.” On February 28, 2014, the Board lifted the stay and informed the parties that it would proceed to decision.

The record developed before the Board

The record before the Board consists of the NCD record, the briefs submitted by the AP and the amici and evidence submitted by the AP and one of the amici, the Human Rights Campaign. Since neither party submitted argument or evidence (except for the CVs) after the Board’s Ruling, the Board treats the AP statement as the AP’s brief in this appeal.¹¹ The AP submitted written declarations made under penalty of perjury from a clinical psychologist and a physician, and two notarized physician letters submitted to an Administrative Law Judge in the Department of Health and Human Services Office of Medicare Hearings and Appeals in another matter. The AP described the witnesses, who are active in the field of treating transgender persons, as experts and submitted their resumes or CVs. AP Statement at 9; AP complaint; AP/CMS e-mail (Jan. 7, 2014).

⁹ The NCD Ruling is at <http://www.hhs.gov/dab/decisions/dabdecisions/ncd1403.pdf>.

¹⁰ The Board also published on its website notice providing an additional time period for interested parties to submit participation requests; none were received.

¹¹ Most of the AP’s evidence other than witness statements is an appendix of sources the clinical psychologist cited in her declaration. We refer to these materials as the AP’s exhibits (AP Exs.) and cite to the page numbers used in the publications in which they appeared. In addition, the physician’s declaration includes an appendix of 20 unnumbered pages of insurance regulations from four states and the District of Columbia barring exclusion of sex reassignment surgery as medically necessary treatment for severe gender dysphoria. One of the amici, the Human Rights Campaign, submitted 62 exhibits with its brief (“HRC Exs.”).

CMS did not challenge the witnesses' qualifications as experts or seek to cross-examine them. We summarize their qualifications when we address their testimony below. In this decision we use the term "new evidence" to refer to the evidence submitted to us by the AP and amici to distinguish it from the evidence used to support the NCD which, as noted, consists principally of the 1981 report. Under the regulatory definition in 42 C.F.R. § 426.110, "new evidence" would also include any evidence submitted by CMS in response to an NCD complaint that was not considered by CMS before the NCD was issued. In this case, however, as we discuss below, CMS submitted no "new evidence."

Standard of review

The Board "evaluate[s] the reasonableness" of an NCD by determining whether it "is valid [or] is not valid under the reasonableness standard," which requires us to uphold the NCD "if the findings of fact, interpretations of law, and applications of fact to law by ... CMS are reasonable" based on the NCD record and the relevant record developed before us. Act § 1869(f)(1)(A)(iii); 42 C.F.R. §§ 426.110, 426.531(a), 426.550(a). The Board "defer[s] only to the reasonable findings of fact, reasonable interpretations of law, and reasonable applications of fact to law by the Secretary." Act § 1869(f)(1)(A)(iii); 42 C.F.R. § 426.505(b).

During the review, the aggrieved party bears the burden of proof and the burden of persuasion for the issues raised in an NCD complaint; the burden of persuasion is judged by a preponderance of the evidence. 42 C.F.R. § 426.330. CMS has explained that "[s]o long as the outcome [in the NCD] is one that could be reached by a rational person, based on the evidence in the record as a whole (including logical inferences drawn from that evidence), the determination must be upheld," and that if CMS "has a logical reason as to why some evidence is given more weight than other evidence," the Board "may not overturn the determination simply because they would have accorded more weight to the evidence in support of coverage." 68 Fed. Reg. at 63,703.

Analysis

The NCD is invalid because a preponderance of the evidence in the record as a whole supports a conclusion that the NCD's stated bases for its blanket denial of coverage for transsexual surgery are not reasonable.

As previously stated, the NCD was based principally on the 1981 report findings that the safety and effectiveness of transsexual surgery had not been proven. The AP argues that these findings are not "supportable by the current state of medical science" and "not reasonable in light of the current state of scientific and clinical evidence and current medical standards of care" and are contradicted by studies conducted in the 32 years since the 1981 report. AP Statement at 6-7, 14. The amici made similar arguments. *See, e.g.,* WPATH Br. at 13 ("since [the NCD] was issued, it has been repeatedly

demonstrated that SRS [sex reassignment surgery] is safe, effective, and indisputably necessary treatment for certain individuals with severe GID [gender identity disorder]”). As we discuss below, the new evidence, which is unchallenged, indicates that the bases stated in the NCD and the NCD record for denying coverage, even assuming they were reasonable when the NCD was issued, are no longer reasonable.

A. The fact that the new evidence is unchallenged and the NCD record undefended is significant.

As we stated earlier, the AP has the burden of proof by a preponderance of the evidence that an NCD is invalid under a reasonableness standard. In deciding whether the AP has met this burden, we must weigh the evidence in the record before us. Thus, we consider it important to note at the outset that the only evidence before us, other than the record for the NCD, which consists principally of the 1981 report, is the new evidence submitted by the AP and the amicus HRC. CMS submitted the NCD record, as it was required to do, but has not argued that that record or any other evidence supports the NCD. CMS also did not elect to cross-examine the AP’s witnesses, has not challenged their testimony or professional qualifications and joined the AP in asking the Board to decide the appeal based on the written record. *See* AP/CMS e-mail (Jan. 7, 2014). The preamble to the regulations that implement the NCD statute states that the “reasonableness standard . . . recognizes the expertise of . . . CMS in the Medicare program—specifically, in the area of coverage requiring the exercise of clinical or scientific judgment.” 68 Fed. Reg. at 63,703 (emphasis added). Accordingly, in determining whether the NCD is valid under the reasonableness standard, we must accord some deference to CMS’s position, and its decision not to defend the NCD or challenge the new evidence in this case has some significance for our decision-making.

Apart from the absence of any challenge to the new evidence or defense of the NCD record, we find the new evidence credible and persuasive on its face.¹² We have no difficulty concluding that the new evidence, which includes medical studies published in the more than 32 years since issuance of the 1981 report underlying the NCD, outweighs the NCD record and demonstrates that transsexual surgery is safe and effective and not experimental. Thus, as we discuss below, the grounds for the NCD’s exclusion of coverage are not reasonable, and the NCD is invalid.

¹² For this reason, we found it unnecessary to exercise our independent authority to “consult with appropriate scientific or clinical experts concerning clinical and scientific evidence.” *See* 42 C.F.R. § 426.531(b).

B. The new evidence indicates acceptance of criteria for diagnosing transsexualism.

Transsexual surgery is a treatment option for the medical condition of transsexualism. The NCD recognized that transsexualism is a diagnosed medical condition. The 1981 report stated that transsexualism “is defined as an overwhelming desire to change anatomic sex stemming from the fixed conviction that one is a member of the opposite sex.” NCD Record at 13, citing Dorland’s Illustrated Medical Dictionary, 25th ed. The 1981 report recognized that the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders issued in 1980 (DSM III) had “included for the first time the diagnostic category of ‘Transsexualism.’” NCD Record at 13. Nonetheless, the 1981 report expressed concern that diagnosing transsexualism was “problematic” because, the report contended, the criteria for establishing the diagnosis “vary from center to center and have changed over time.” NCD Record at 14.

One of the AP’s expert witnesses, Randi Ettner, Ph.D., a clinical psychologist, testified that the expressed basis for this concern is “completely untrue now.” Ettner Supp. Decl. at ¶ 5. Dr. Ettner stated that “Gender Identity Disorder is a serious medical condition codified in the International Classification of Diseases (10th revision; World Health Organization) and the [DSM].”¹³ Ettner Decl. at ¶ 10; *see also* Ettner Supp. Decl. at ¶ 6 (similar testimony). She described the condition as follows:

The disorder is characterized by intense and persistent discomfort with one’s primary and secondary sex characteristics—one’s birth sex. The suffering that arises is often described as “being trapped in the wrong body.” The psychiatric term for this severe and unremitting emotional pain is “gender dysphoria.”

Ettner Decl. at ¶ 10. Dr. Ettner’s declaration and CV state that she has a doctorate in psychology, has evaluated or treated between 2,500 and 3,000 individuals with GID and mental health issues related to gender variance, has published three books, including *Principles of Transgender Medicine and Surgery*, has authored articles in peer-reviewed journals, and is a member of the board of directors of the World Professional Association for Transgender Health (WPATH) and an author of the WPATH Standards of Care for

¹³ The record indicates that the term “transsexualism” that was used in the NCD and the DSM-III was succeeded in the DSM-IV and DSM-V by the terms “Gender Identity Disorder” (GID) and “gender dysphoria.” AP Statement at 1 n.1; Ettner Supp. Decl. at ¶ 6; Hsiao Decl. at ¶ 11; AP Ex. 7, at 208; WPATH Br. at 2 n.3. In this decision, we use the term “transsexualism” because it is used in the NCD, but our decision should be read as encompassing the successor terminology as well.

the Health of Transsexual, Transgender, and Gender-Nonconforming People. *Id.* at ¶¶ 3-6; *see also Sundstrom v. Frank*, 630 F. Supp. 2d 974, 986-87 (E.D.Wis. 2007) (“Dr. Ettner’s experience speaks for itself ... the doctor has conducted research and has been an instructor specializing in the etiology, diagnosis and treatment of GID [and] is the editor of a medical textbook in which she wrote the chapter of that book on the etiology of GID. The court finds that Dr. Ettner is sufficiently qualified to provide expert testimony.”).

We find nothing in the new evidence that would undercut Dr. Ettner’s statement. The DSM-IV-TR (text revision), published in 2000, continues to recognize “transsexualism” as a diagnosed medical condition, although it refers to the same disorder as GID and identifies criteria for diagnosing GID in adolescents and adults that are consistent with Dr. Ettner’s description, albeit more detailed. The criteria include “strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex)” that is “manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex;” “[p]ersistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex” that is “manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex;” and “[t]he disturbance is not concurrent with a physical intersex condition.” AP Ex. 4, at 581. The DSM-IV-TR states that if GID is present in adults, “[t]he disturbance can be so pervasive that the mental lives of some individuals revolve only around those activities that lessen gender distress.” *Id.* at 576, 78. The WPATH brief indicates that transsexualism or GID remains a diagnostic category in the fifth edition of the DSM issued in 2013 (DSM-V), which uses the term “Gender Dysphoria.” WPATH Br. at 2, n.3.

The DSM has been recognized as a primary diagnostic tool of American psychiatry. *See O’Donnabhain v. Comm’r of Internal Revenue*, 134 T.C. 34, at 60 (2010) (stating “all three experts agree [that the DSM-IV-TR] is the primary diagnostic tool of American psychiatry”); *see also* AP Ex. 3, at 1¹⁴ (resolution of American Medical Association House of Delegates noting the DSM description of GID as “a persistent discomfort with one’s assigned sex and with one’s primary and secondary sex characteristics, which causes intense emotional pain and suffering” that “if left untreated, can result in clinically significant psychological distress, dysfunction, debilitating depression and, for some people without access to appropriate medical care and treatment, suicidality and death”).

¹⁴ American Medical Association House of Delegates, *Resolution 122 (A-08), Removing Financial Barriers to Care for Transgender Patients* (2008).

We conclude that to the extent the NCD was based on concerns expressed in the NCD record about problems diagnosing transsexualism, that concern is unreasonable based on the new evidence.

*C. The new evidence indicates that transsexual surgery is safe.*¹⁵

The 1981 report stated that transsexual surgery “cannot be considered safe because of the high complication rates.” NCD Record at 18. The 1981 report identified surgical complications including “rectovaginal fistulas, perineal abscesses, introital and deep vaginal stenosis, and vaginal shortening” in male-to-female (MF) patients, and “rejection of the testicular implants, scrotal fusion, and phalloplasty infections” in female-to-male (FM) patients, and states that “[m]ultiple complications for individual patients and secondary surgeries to correct complications or to improve on undesirable results are not uncommon.” *Id.* at 15 (citations omitted). The AP argues that “advancements in surgical techniques have dramatically reduced the risk of complications from sex reassignment surgery and the rates of serious complications from such surgeries are low” and that the studies cited in the 1981 report “evaluated outdated surgical techniques that have been replaced with improved, safer procedures.” AP Statement at 7, 10. The new evidence supports the AP.

Expert witness Katherine Hsiao, M.D., testified that hysterectomies and mastectomies are common procedures used to treat gender GID in transgender men (FM) and “are routinely performed in other contexts, such as in cases of breast cancer, ovarian cancer, uterine cancer and/or cervical cancer” Hsiao Decl. at ¶ 11. These procedures, she stated, “have low rates of complications” and are “generally identical whether performed on transgender men to treat gender dysphoria or to treat women for these other conditions.”¹⁶ *Id.* Dr. Hsiao also stated that “insurance companies routinely cover the costs associated” with hysterectomies. *Id.* Dr. Hsiao testified that based on her own practice of providing surgery to transgender men, “gender affirming surgeries for transgender men are extremely safe and have very low rates of serious complications,”

¹⁵ We are unable to discuss in the space of this decision all of the new evidence and see no need to do so since it is all unchallenged. However, we find nothing in the new evidence not discussed that would alter our conclusion that the NCD is invalid, at least absent argument or counter-evidence from CMS. We have attached to this decision an Overview of the Scientific Literature in the New Evidence.

¹⁶ Dr. Hsiao testified without contradiction that a “serious complication” of surgery—

is generally understood among surgeons to include death, conditions requiring an unplanned admission to the Intensive Care Unit or unplanned readmission to the hospital within 30 days, severe hemorrhage requiring transfusion of several units of blood product, permanent disability, an intraoperative injury requiring an unplanned intervention during the surgical procedure, permanent brain damage, or cardiac arrest.

Hsiao Decl. at ¶ 9.

that she has performed hysterectomies for transgender men for the past ten years and that those procedures “are generally identical to the ones I perform on women to treat early cancer or other conditions.” *Id.* at ¶ 20. Dr. Hsiao reports having “typically performed multiple obstetrical, gynecologic, or other pelvic surgeries every week, including but not limited to hysterectomies and other advanced pelvic surgeries targeting the reproductive system and adjacent organs” *Id.* at ¶ 6. Dr. Hsiao’s declaration and CV indicate that she is certified by the American Board of Obstetrics and Gynecology, is the chief of the division of gynecology and the director of Ob/Gyn resident education at a California medical center and an assistant clinical professor in the department of obstetrics, gynecology and reproductive medicine at the University of California at San Francisco. *Id.* at ¶¶ 3-6; CV.

Dr. Hsiao further stated, regarding MF transsexual surgery, that she has been part of a surgical team that performed surgery to create a neovagina in women born with a congenital “complete or partial absence of a vagina, cervix, and uterus,” a condition called Mayer-Rokitansky-Kuster-Hauser syndrome, or MRKH. Hsiao Decl. at ¶ 12. She stated that this procedure has “a low rate of complications,” and that the associated surgical costs are, in her experience, “routinely cover[ed]” by insurance companies for women born with MRKH. She stated that while women with MRKH “can never have biological children . . . the role of surgery is essential to affirm their gender identity and to align their anatomy with that identity.” *Id.*

Dr. Ettner stated that “[t]here is no scientific or medical basis” for the NCD’s statement that sex reassignment surgery has not been proven safe and has a high rate of serious complications; that the “[r]ates of complications during and after sex reassignment surgery are relatively low, and most complications are minor;” and that the risk of complications “has, moreover, been dramatically reduced since 1985.” Ettner Decl. at ¶¶ 32, 34. Dr. Ettner testified that during eight years at the Chicago Gender Clinic she “regularly consulted with our surgeon” and is “aware of only two major surgical complications, both of which were immediately repaired.” *Id.* at ¶ 36. She stated that the clinic “as a whole has a 12 percent complication rate for genital surgery” and that “the vast majority of those complications [were] minor, all were easily corrected, and none involved surgical site infection or readmission.” *Id.* Dr. Ettner stated the 1981 report’s discussion of surgical complication rates was “outdated and irrelevant based on current medical practices and procedures.” Ettner Supp. Decl. at ¶ 9. In particular, she stated that one of the studies cited in the 1981 report’s discussion of complications (Laub & Fisk 1974) reflected the use of a MF surgical technique that “led to unacceptably high rates of fistulae and other complications” and was later abandoned by the study’s authors. *Id.* at ¶ 10.

Another of the AP’s expert witnesses, Marci L. Bowers, M.D., stated in her notarized letter that in her experience of performing gender-related surgeries, transsexual surgery “does not have a higher rate of complication than any other surgery, and in fact has very

few complications, which are mainly minor in nature.” Bowers Letter at 1 (Mar. 5, 2013), Att. to AP Statement. Dr. Bowers stated that she performs approximately 220 gender-related surgeries annually and has performed over 1000 “Male to Female Gender Corrective Surgeries.” *Id.* Her CV indicates that she has served as the Chair of the Department of Obstetrics and Gynecology at the Swedish (Providence) Medical Center in Seattle.

The fourth expert witness, Sherman N. Leis, M.D., stated that he personally “perform[s] several gender reassignment procedures each week” and has “seen only relatively minor complications which are easily treated” and has “thus far seen no life threatening complications from any of the transgender surgeries” he has performed. Leis Letter at 2 (Feb. 28, 2013), Att. to AP Statement. Dr. Leis’s letter and CV indicate that he is Board-certified in plastic and reconstructive surgery and in general surgery. *Id.* at 1.

The testimony of Drs. Ettner and Hsiao is based on studies as well as personal experience. Dr. Hsiao testified that she reviewed five studies in the AP exhibits “that include complication rate data and information for gender affirming surgeries performed in recent years” and that “[n]one of these five studies reported high rates of serious complications.” Hsiao Decl. at ¶¶ 13-14, citing studies at AP Exs. 2, 9, 14, 21, 28. She stated that “almost all of the complications listed in these studies, such as urinary incontinence or retention, stenosis or stricture, bleeding, recto-vaginal fistula, and partial necrosis, are not specific to sex reassignment surgeries, but rather are known potential side effects of any type of urogenital surgery which are covered by Medicare.” *Id.* at ¶ 15. She further testified that “every complication tracked in [Jarolim, et al. (2009)] for instance, falls into this category and none of them are serious;” that “[t]he Spehr (2007) study includes similar types of complications at very low rates;” and that “none of the complications listed in Lawrence (2006) are serious and many of them are consistent with what would be potential, expected outcomes for any urogenital surgery.” *Id.* at 15-17, citing studies at AP Exs. 14,¹⁷ 21,¹⁸ 28.¹⁹ She also stated that of the four “potentially serious” complications noted in the Amend (2013) study of 24 MF patients, none “were serious as that term is generally understood.” *Id.* at ¶ 14, citing study at AP Ex. 2.²⁰

¹⁷ Ladislav Jarolim, et al., *Gender Reassignment Surgery in Male-to-Female Transsexualism: A Retrospective 3-Month Follow-up Study with Anatomical Remarks*, 6 J. Sex. Med. 1635-44 (2009).

¹⁸ Anne A. Lawrence, *Patient-Reported Complications and Functional Outcomes of Male-to-Female Sex Reassignment Surgery*, 35 Arch. Sex. Behav. 717-27 (2006).

¹⁹ Christiane Spehr, *Male-to-Female Sex Reassignment Surgery in Transsexuals*, 10 Int’l J. Transgenderism 25-37 (2007).

²⁰ Bastian Amend, et al., *Surgical Reconstruction for Male-to-Female Sex Reassignment*, 64 Eur. Urol. 1-9 (2013).

Dr. Hsiao further stated that Eldh et al. (1997) compared complication rates for surgeries performed before and after 1986 and showed that “[n]early all of the surgical complication rates decreased significantly over time.” Hsiao Decl. at ¶ 18, citing study at AP Ex. 9.²¹ Dr. Hsiao stated that “fistulas, in particular, which are a risk of many urogenital surgeries, decreased from 18 percent in surgeries before 1986 to only 1 percent between 1986 and 1995,” and that “the only fistula that occurred after 1985 ‘closed spontaneously,’ meaning without the need for any medical intervention.” *Id.* Eldh, Dr. Hsiao stated, showed that “[t]here is not a high rate of serious complications in any of the surgeries performed after 1986” and she noted that “there have been nearly 20 years of additional surgical progress since the last surgery tracked.” *Id.*

Dr. Ettner cited the same five studies as showing that surgical outcomes were “far superior” after 1985 due to “improvements in technique, shortened hospital stays and improvements in postoperative care,” that significant surgical complications were uncommon; that only a low percentage of patients experienced complications, which were successfully resolved; and that “the complication rate is low and most complications can be overcome by adequate correctional interventions.” Ettner Decl. at ¶¶ 34-35.

We find no reason to discount the opinions of these experts or their representations regarding the findings in the studies they cite. We have conducted our own review of the studies cited by Dr. Hsiao and Dr. Ettner and find them consistent with these opinions and representations. We note, for example, that Eldh, which divided the study group into those operated on before 1986 and those operated on from 1986–1995, made findings tending to support these expert opinions. The Eldh study states:

After 1985 the outcome of surgery became much better not only because of changes in management but also because of improvements in surgical technique, preoperative planning, and postoperative treatment. Total time spent in hospital decreased dramatically after 1985 because the number of procedures was less and the rate of early and late postoperative complications dropped. Haemorrhage and haematoma were common in both groups, predominantly originating from the spongy tissue of the urethra. Infections occurred less often in the late group perhaps as a result of preoperative antibiotic prophylaxis. Serious complications like fistula formation and partial flap necrosis were rare after 1985, though they were common before then. The reason for the lower fistula rate in the later group may be ascribed to better anatomical knowledge of this region and a more precise surgical technique. There was only one rectovaginal fistula after 1985 and this fistula closed spontaneously.

²¹ Jan Eldh, et al., *Long-Term Follow Up After Sex Reassignment Surgery*, 31 Scand. J. Plast. Reconstr. Surg. Hand Surg. 39-45 (1997).

AP Ex. 9, at 44. Dr. Hsiao stated that those findings are “consistent with what I would expect to find when comparing surgeries, and surgical techniques, over a long period of time.” Hsiao Decl. at ¶ 18; *see also* WPATH Br. at 9-10 (citing Eldh and stating that “while early sex reassignment surgeries were sometimes accompanied by serious complications like fistulas or necrotic tissue, the rate of such complications has dropped dramatically with the advent of more sophisticated surgical techniques, among other reasons”).

We conclude that the AP has shown that the NCD’s statement that transsexual surgery is unsafe and has a high rate of complications is not reasonable in light of the evolution of surgical techniques and the studies of outcomes discussed in the unchallenged new evidence presented here.

D. The new evidence indicates that transsexual surgery is an effective treatment option in appropriate cases.²²

1. The expert testimony and studies on which the experts rely support the surgery’s effectiveness.

The AP argues that studies conducted after the 1981 report was issued confirm that transsexual surgery is an effective treatment for persons with severe gender dysphoria, and the expert testimony and studies support that argument. AP Statement at 7-8.

Dr. Ettner testified that “[b]ased on decades of extensive scientific and clinical research, the medical community has reached the consensus that altering a transsexual individual’s primary and secondary sex characteristics is a safe and effective treatment for persons with severe Gender Identity Disorder.” Ettner Decl. at ¶ 13.²³ With regard to effectiveness in particular, Dr. Ettner testified that “more than three decades of research confirms that sex reassignment surgery is therapeutic and therefore an effective treatment for Gender Identity Disorder” and that “for many patients with severe Gender Identity

²² We use the term “appropriate cases” because we do not read the new evidence as necessarily stating that transsexual surgery is appropriate in all cases of transsexualism, and our conclusion that the NCD’s blanket preclusion of Medicare coverage for transsexual surgery is invalid does not require a finding to that effect. However, it is worth noting that WPATH has developed, in its standards of care, criteria for the use of different transsexual surgical procedures. *See, e.g.,* WPATH “[c]riteria for hysterectomy and salpingo-oophorectomy in [FM] patients and for orchiectomy in [MF] patients.” AP Ex. 7, at 202 (E. Coleman, et al., *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People*, Version 7, 13 Int’l J. Transgenderism 165–232 (2011)).

²³ Dr. Ettner in her declaration focuses on genital surgery for the male-to-female (MF) transsexual. *See* Ettner Decl. at ¶ 8. Dr. Hsiao’s testimony addressed procedures performed on FM patients. Hsiao Decl. at ¶¶ 7, 11, 20-21.

Disorder, sex reassignment surgery is the only effective treatment.” *Id.* at ¶ 19. She concluded that “[t]he NCD’s determination regarding efficacy is not reasonably supported by scientific or clinical evidence, or standards of professional practice, and fails to take into account the robust body of research establishing that surgery relieves, and very often completely eliminates, gender dysphoria.” *Id.* at ¶ 31.

Dr. Bowers stated that “[m]any patients report a dramatic improvement in mental health following surgery, and patients have been able to become productive members of society, no longer disabled with severe depression and gender dysphoria.” Bowers Letter at 1. She concluded that “Gender Corrective Surgery has been shown to be a life-saving procedure, and is unequivocally medically necessary.” *Id.* Dr. Leis stated that “[m]edical literature reports a dramatic drop in the incidence of depression and suicide attempt[s] by individuals who have undergone gender reassignment, indicating that many lives have been saved because of this surgery,” that “there is a very low incidence of ‘regret’” of “only about 1% of patients who have had gender reassignment surgery” and that “I personally have never had a single patient who has regretted having this surgery.” Leis Letter at 2.

Dr. Ettner cited 20 studies published between 1987 and 2010 as showing the effectiveness of transsexual surgery. Ettner Decl. at ¶¶ 20-26, 28-30. She emphasized three studies, two of which were published in 1998 and 2007 and analyze other studies of the treatment of transsexuals published during the years 1961 to 1991 and 1990 to 2007, respectively. *Id.* at ¶¶ 20-22, citing studies at AP Exs. 10, 25, 27; *see also* WPATH Br. at 7-8 (discussing the same three studies). The 1998 study (Pfafflin & Junge) reviewed “30 years of international follow-up studies of approximately two thousand persons who had undergone sex reassignment surgery” including more than 70 individual studies and eight published reviews from four continents. AP Ex. 25 at unnumbered page 1.²⁴ As “general results,” the researchers in the 1998 study stated that the studies they reviewed concluded “that gender reassigning treatments are effective,” that positive, desired results outweigh the negative or non-desired effects, and that “[p]robably the most important change that is found in most research is the increase of subjective satisfaction [which] contrasts markedly to the subjectively unsatisfactory start position of the patients.” *Id.* at 45, 49. The study’s summary, which it qualified as a “simplification,” stated that the studies reviewed show that “[i]n over 80 qualitatively different case studies and reviews from 12 countries, it has been demonstrated during the last 30 years that the treatment that includes the whole process of gender reassignment is effective.” *Id.* at 66. The summary stated that all “follow-up studies mostly found the desired effects” the most important of

²⁴ Friedemann Pfafflin & Astrid Junge, *Sex Reassignment: Thirty Years of International Follow-Up Studies After Sex Reassignment Surgery: A Comprehensive Review 1961-1991* (Roberta B. Jacobson & Alf B. Meier trans., 1998) (1992) (<http://web.archive.org/web/20061218132346/http://www.symposium.com/ijt/pfaefflin/1000.htm>, accessed May 29, 2014).

which the patients felt were “the lessening of suffering” and “desired changes in the areas of partnership and sexual experience, mental stability and socio-economic functioning level.” *Id.* at 66-67.

The 2007 study, Gijs & Brewaeys, which examined the results of 18 studies published between 1990 and 2006, states that sex reassignment “is the most appropriate treatment to alleviate the suffering of extremely gender dysphoric individuals” and that “96% of the persons who underwent [surgery] were satisfied and regret was rare.” AP Ex. 10, at 215, cited in Ettner Decl. at ¶ 22, WPATH Br. at 7.²⁵ Two of the reviewed studies showed that “[s]uicidality was significantly reduced postoperatively” and that in MF patients there were no suicide attempts after surgery as opposed to three attempts before surgery. AP Ex. 10, at 188, 192.

Dr. Ettner and WPATH also cited what Dr. Ettner described as “a large-scale prospective study” finding “that after surgery there was ‘a virtual absence of gender dysphoria’ in the cohort and that the ‘results substantiate previous conclusions that sex reassignment is effective.’” Ettner Decl. at ¶ 21, citing Smith et al. (2005), AP Ex. 27;²⁶ WPATH Br. at 8. Dr. Ettner concluded that Smith et al. and other studies have, variously, “shown that by alleviating the suffering and dysfunction caused by severe gender dysphoria, sex reassignment surgery improves virtually every facet of a patient’s life,” including “satisfaction with interpersonal relationships and improved social functioning,” “improvement in self-image and satisfaction with body and physical appearance,” and “greater acceptance and integration into the family[.]” Ettner Decl. at ¶ 24, citing studies at AP Exs. 1, 12, 15, 19, 22, 26, 27, 30. She also cited nine studies as having “shown that surgery improves patients’ abilities to initiate and maintain intimate relationships.” *Id.* at ¶ 25, citing studies at AP Exs. 8, 13, 14, 16, 20-22, 26, 27.

Based on our own review of the cited studies, we find no reason to question the expert testimony about them. In general, the studies included interviewing post-operative patients with a variety of surveys or questionnaires to assess changes in different aspects of their lives and psychological symptoms following surgery. The studies also generally used statistical techniques to assess the results. The studies were conducted in countries including the United States, Canada, Sweden, the Czech Republic, Israel, Brazil, The Netherlands, and Belgium.

²⁵ Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges*, 18 Ann. Rev. Sex Res. 178-224 (2007).

²⁶ Yolanda L.S. Smith et al., *Sex Reassignment: Outcomes and Predictors of Treatment for Adolescent and Adult Transsexuals*, 35 Psychol. Med. 89-99 (2005).

We note that these studies are scientific writings and do not make sweeping pronouncements or claim discoveries beyond possible doubt. Indeed, the authors sometimes qualify the results and caution against drawing overly broad and simplistic conclusions. *See, e.g.*, AP Ex. 25, at 66 (Pfafflin & Junge, qualifying the study's summary of its conclusion as a simplification). This, in our view, enhances their facial credibility. Nonetheless, even keeping in mind the possible limitations of these studies, they support the AP's position that transsexual surgery has gained broad acceptance in the medical community.

2. *The 1981 report's expressed concern about an alleged lack of controlled, long-term studies is not reasonable in light of the new evidence.*

The 1981 report summarized the findings of nine studies on “[t]he result or outcome of” transsexual surgery. NCD record at 15-18. With respect to those studies, the report stated that “surgical complications are frequent, and a very small number of post-surgical suicides and psychotic breakdowns are reported.” *Id.* at 17-18. However, the report also acknowledged that eight of those nine studies “report that most transsexuals show improved adjustment on a variety of criteria after sex reassignment surgery, and that “[i]n all of these studies the large majority of those who received surgery report that they are personally satisfied with the change[.]” NCD Record at 17. Notwithstanding its discussion of these studies, the 1981 report (and the NCD) cited an alleged “lack of well controlled, long term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism” as a ground for finding the procedures “experimental.” *Id.* at 19. The 1981 report did not define “long term” for the purpose of assigning weight to study results and the NCD record provided no clarification of that phrase. The 1981 report noted “post-operative followup” and “followup” times for eight of the nine studies on the outcomes of surgery, with “average,” “mean” or “median” periods ranging from 25 months to over eight years, and individual periods from three months to 13 years. NCD Record at 15-17. If these studies do not qualify as acceptable long-term studies, the basis for such a conclusion is not adequately explained in the NCD record.

Even assuming the studies cited in the 1981 report could be viewed as not sufficiently “long-term,” Dr. Ettner stated that “there are numerous long-term follow-up studies on surgical treatment demonstrating that surgeries are effective and have low complication rates” and, as discussed above, her testimony cited some of those studies. Ettner Decl. at ¶ 26. CMS does not challenge this statement, and we find no reason to question it. We note that the participants in one study Dr. Ettner cited had a mean interval since

vaginoplasty of 75.46 months. AP Ex. 30, at 754.²⁷ We also note that the 18 studies published between 1990 and 2006 and encompassing 807 MF and FM patients analyzed in Gijs & Brewaeys (2007) had mean follow-up durations ranging from six months to as long as (in one study) 168 months. AP Ex. 10, at 186-87.²⁸ Additionally, two studies Dr. Ettner cited appear to be long term in that they studied patients who had undergone surgery during periods of 14 and 20 years, respectively. AP Exs. 13,²⁹ 29.³⁰ Those studies reported favorable overall results.

Dr. Ettner also testified that two studies from 1987 and 1990 used control groups and found improved psychosocial outcomes in surgery patients. Ettner Decl. at ¶¶ 28-30. In the 1990 study, she stated, MF patients were “matched for family and psychiatric histories and severity of the [GID] diagnosis” and “randomly assigned either to immediately undergo surgery, or be placed on a waiting list for two years.” *Id.* at ¶ 29, citing study at AP Ex. 23.³¹ The study found that patients who underwent surgery “demonstrated dramatically improved psychosocial outcomes, compared to the still-waiting controls” and “were more active socially and had significantly fewer psychiatric symptoms.” *Id.*; see also WPATH Br. at 8 (study found “comparative improvements in neurotic symptoms and social activity for the group receiving surgery”). Dr. Ettner described the 1990 study as the “best example of a well-controlled investigation.” Ettner Decl. at ¶ 29. Dr. Ettner also described a 1987 study comparing transsexuals who had undergone surgery with “those who had not, but were otherwise matched (control group)” as finding that “the patients who underwent surgery were better adjusted psychosocially, had improved financial circumstances, and reported increased satisfaction with sexual experiences, as compared to the unoperated group.” *Id.* at ¶ 30, citing study at AP Ex. 17.³²

²⁷ Steven Weyers, M.D., et al., *Long-term Assessment of the Physical, Mental, and Sexual Health Among Transsexual Women*, J. Sex. Med. 752-60 (2009).

²⁸ Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges*, 18 Ann. Rev. Sex Res. 178-224 (2007).

²⁹ Ciro Imbimbo, M.D. Ph.D., et al., *A Report from a Single Institute’s 14-Year Experience in Treatment of Male-to-Female Transsexuals*, 6 J. Sex. Med. 2736-45 (2009).

³⁰ Svetlana Vujovic, M.D. Ph.D., et al., *Transsexualism in Serbia: A Twenty-Year Follow-Up Study*, 6 J. Sex. Med. 1018-23 (2009).

³¹ Charles Mate-Kole, et al., *A Controlled Study of Psychological and Social Change After Surgical Gender Reassignment in Selected Male Transsexuals*, 157 Brit. J. Psychiatry 261-64 (1990).

³² G. Kockott, M.D. & E. M. Fahrner, Ph.D., *Transsexuals Who Have Not Undergone Surgery: A Follow-Up Study*, 16 Archives of Sexual Behavior 511-22 (1987).

Nothing in the record puts into question the authoritativeness of the studies cited in the new evidence based on methodology (or any other ground). Even if questions about methodology had been raised, we would be hard pressed to find that this alone would justify our not crediting the new evidence that transsexual surgery is effective and safe. This is particularly true since the 1981 report itself suggested it might be impossible to find the kind of adequate control groups needed to assuage this criticism. *See* NCD Record at 18 (stating the need for adequate control groups and stating “perhaps this is impossible.”). We note that in the local coverage determination (LCD) context, CMS guidance for contractors states that the determinations “shall be based on the strongest evidence available.” CMS Medicare Program Integrity Manual (MPIM), CMS Pub. 100-08, Ch. 13, § 13.7.1.³³ While the guidance states a “preference” for “[p]ublished authoritative evidence derived from definitive randomized clinical trials or other definitive studies . . .,” it also includes as evidence meeting that standard, “[g]eneral acceptance by the medical community (standard of practice), as supported by sound medical evidence”³⁴ *Id.* In *LCD Complaint: Homeopathic Med. & Transfer Factor*, DAB No. 2315 (2010), the Board relied on that guidance when rejecting the argument that a certain type of controlled study was the sole basis on which a determination of medical necessity could be supported. The Board stated, “[a]s the [CMS guidance] explains, general acceptance in the medical community may be sufficient if it has scientific support.” DAB No. 2315, at 34. While the guidance applies to contractors, who develop LCDs but not NCDs, it is instructive here as representing CMS’s determination of the type of evidence that may support Medicare coverage. Regardless of whether the new evidence here meets the first option for meeting the evidentiary standard set forth in the guidance (and CMS does not assert that it does not), it clearly meets the second option because it indicates a consensus among researchers and mainstream medical organizations that transsexual surgery is an effective, safe and medically necessary treatment for transsexualism.

Based on the record as a whole, including the new evidence discussed above, we conclude that the AP has shown that transsexual surgery is an effective treatment option for transsexualism in appropriate cases.

³³ CMS Manuals are available at <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs.html>, accessed May 14, 2014.

³⁴ The guidance further provides that the “sound medical evidence” supporting this “general acceptance” should be based on “[s]cientific data or research studies published in peer-reviewed medical journals; . . . [c]onsensus of expert medical opinion (i.e., recognized authorities in the field); or . . . [m]edical opinion derived from consultations with medical associations or other health care experts.” MPIM § 13.7.1.

E. The new evidence indicates that the NCD’s rationale for considering the surgery experimental is not valid.

The NCD asserted that transsexual surgery was considered experimental because it had not been shown to be safe and effective.³⁵ The 1981 report stated that transsexual surgery “must be considered still experimental” because “[t]he safety and effectiveness of transsexual surgery as a treatment of transsexualism is not proven and is questioned.” NCD Record at 19. As discussed above, the unchallenged new evidence indicates that transsexual surgery is a safe and effective treatment option for transsexualism in appropriate cases. Accordingly, the NCD’s reasons for asserting that transsexual surgery was experimental are no longer valid.

In addition, the new evidence independently indicates that transsexual surgery is not considered experimental in a broader sense relating to its acceptance as a treatment for transsexualism. Dr. Bowers stated that “[m]any thousands of gender corrective surgeries have been performed worldwide for decades, and this treatment is in no way experimental.” Bowers Letter at 1. Dr. Hsiao testified that there is “no scientific or medical basis for [the NCD’s] description of gender affirming surgeries as ‘experimental.’” Hsiao Decl. at ¶ 22. Dr. Hsiao, as noted, stated that some of the procedures involved in transsexual surgery are routinely performed in other contexts, and that surgery to create a neovagina is performed on women born MRKH. Hsiao Decl. at ¶¶ 11, 12; see Ettner Supp. Decl. at ¶ 15 (“mastectomies, hysterectomies and salpingo-oophorectomies, which are ... excluded from coverage under [the NCD] are performed frequently... when indicated for medical conditions other than gender dysphoria”).

Dr. Hsiao cited the “increasing coverage of sex affirming surgeries by private and public medical plans” and the inclusion of those surgeries “in prominent surgical text books” as showing that “gender affirming surgeries ... are the standard of care and are not experimental.” *Id.* at ¶¶ 23, 24. Dr. Hsiao cited California managed care guidance “clarifying that any attempt ‘to exclude insurance coverage of [] transsexual surgery’” would violate California law, and she stated that Vermont, Colorado, Oregon, and Washington, D.C. “have issued similar insurance directives prohibiting discrimination based on gender identity with respect to healthcare policies.” *Id.* at ¶ 25, citing Letter No. 12-K: Gender Nondiscrimination Requirements, Calif. Dep’t of Managed Health Care

³⁵ “Because of the lack of well controlled, long-term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism, the treatment is considered experimental.” NCD Record at 93.

(Apr. 9, 2013), Ex. A to Hsiao Decl.³⁶ “These events in the private and public sector,” Dr. Hsiao stated, “solidify what the medical community has known for years—that gender affirming surgeries to treat gender dysphoria are evidence-based, medically necessary, and the standard of care for these patients.” *Id.* at ¶ 26.

Dr. Leis stated that gender reassignment surgery “is not experimental and has been performed thousands of times with surgeons around the world and has been proven to be a medically necessary and successful treatment, saving many lives and significantly improving the lives of those who undergo this surgery.” Leis Letter at 2. Dr. Leis also stated that “[m]edical and mental health professionals who are knowledgeable and experienced in this field recognize that counseling or psychotherapy, hormone therapy and genital reassignment surgery are medically necessary treatment modalities for many individuals with [GID]” and that those therapies “are widely accepted treatments for individuals with significant [GID] in the United States and in many other countries.” *Id.* at 1. Dr. Leis also pointed to the acceptance of transsexual surgery procedures “as standard therapy by leading medical and mental health organizations” including the American Medical Association, the National Association of Social Workers, the American Psychological Association, the American Psychiatric Association, “and experts in the field belonging to” WPATH. *Id.* at 2.

HRC stated that its “Corporate Equality Index” annually surveys the “LGBT [lesbian, gay, bisexual and transgender] workplace policies” of “the Fortune 1000 list of the largest publicly traded companies along with American Lawyer Magazine’s top 200 revenue-grossing law firms” and considers “whether these organizations afford transgender-inclusive health care options through at least one firm-wide plan that covers surgical procedures.” HRC Br. at 1, 11-12. HRC stated that in 2002, “zero percent of the rated companies had such plans” but “by 2008, nineteen percent met this criterion, and by 2013, forty-two percent of companies expressly covered” care related to gender reassignment. *Id.* citing HRC Ex. 30, at 28.³⁷

Dr. Bowers, Dr. Hsiao and Dr. Ettner cited acceptance of the WPATH standards of care, which were first published in 1979 and last revised in 2011, as evidence that transsexual surgery is not experimental. Bowers Letter at 1; Hsiao Decl. at ¶ 22; Ettner Decl. at ¶¶ 38, 39; AP Ex. 7, at 165; *see also* AP Ex. 3 (AMA resolution stating that “[h]ealth experts in GID, including WPATH, have rejected the myth that such treatments are “cosmetic” or “experimental” and have recognized that these treatments can provide safe and effective treatment for a serious health condition”). The new evidence indicates that

³⁶ <http://www.dmh.ca.gov/library/reports/news/dl12k.pdf>, accessed May 14, 2014.

³⁷ HRC Corporate Quality Index (2013), available at <http://www.hrc.org/corporate-equality-index>, accessed April 25, 2014.

the WPATH standards of care have attained widespread acceptance.³⁸ See Hsiao Decl. at ¶ 22 (“the WPATH established standards of care for patients with gender dysphoria ... have been endorsed by the American Medical Association, the Endocrine Society, the American Psychological Association, and the American College of Obstetricians and Gynecologists”); AP Ex. 3 (AMA resolution stating that WPATH is “the leading international, interdisciplinary professional organization devoted to the understanding and treatment of gender identity disorders” and that its “internationally accepted Standards of Care for providing medical treatment for people with GID ... are recognized within the medical community to be the standard of care for treating people with GID”). Federal courts have recognized the acceptance of the WPATH standards of care. See, e.g., *De’lonta v. Johnson*, 708 F.3d 520, at 522-23 (4th Cir. 2013) (WPATH standards of care “are the generally accepted protocols for the treatment of GID”); *Glenn v. Brumby*, 724 F. Supp. 2d 1284, at 1289 n.4 (N.D. Ga. 2010) (“there is sufficient evidence that statements of WPATH are accepted in the medical community”).³⁹ The acceptance of the WPATH standards of care also suggests that transsexual surgery is no longer considered experimental.

In its amicus brief, WPATH cited a 2007 study that examined the results of 18 studies published between 1990 and 2006 as showing “that [sex reassignment surgery] can no longer be considered an experimental treatment” and that “it [has] bec[o]me the dominant treatment for transsexuality and the *only* treatment that has been evaluated empirically.” WPATH Br. at 7-8, citing AP Ex. 10, at 214-15.⁴⁰

We note that in addition to stating that transsexual surgery was experimental, the NCD and the 1981 report stated that transsexual surgery was “controversial.” NCD Record at 18 (1981 report stating that “[o]ver and above the medical and scientific issues, it would also appear that transsexual surgery is controversial in our society”). The AP and the new evidence dispute the relevance of this statement. The AP objected that this point relies on two “polemics” that are “are either completely unscientific or fall far outside the scientific mainstream,” and Dr. Ettner stated that the views expressed therein “fall far outside the mainstream psychological, psychiatric, and medical professional consensus,

³⁸ WPATH was “formerly the Harry Benjamin International Gender Dysphoria Association.” Ettner Decl. at ¶ 6. Harry Benjamin, M.D. “was an endocrinologist who in conjunction with mental health professionals in New York did pioneering work in the study of transsexualism.” *O’Donnabhain v. Comm’r of Internal Revenue*, 134 T.C. 34, 37 n.8 (2010). The 1981 report cites a 1966 study by Dr. Benjamin finding a positive outcome from MF transsexual surgery as “perhaps the first report” on transsexual surgery “in the literature.” NCD Record at 15, 21.

³⁹ The general acceptance of a set of standards of care for the treatment of transsexuals appears to render invalid one of the 1981 report criticisms of the studies it discussed, that “therapeutic techniques are not standardized.” NCD Record at 18.

⁴⁰ Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges*, 18 Ann. Rev. Sex Res. 178-224 (2007).

and call into question the objective reasonableness of the NCD.” AP Statement at 15-16; Ettner Supp. Decl. at ¶¶ 17-18. CMS has not asserted that the Board’s decision may be based on factors “over and above the medical and scientific issues” involved. Considerations of social acceptability (or nonacceptability) of medical procedures appear on their face to be antithetical to Medicare’s “medical necessity” inquiry, which is based in science, and such considerations do not enter into our decision that the NCD is not valid.

For the reasons stated above, we conclude that citing the alleged “experimental” nature of transsexual surgery as a basis for noncoverage of all transsexual surgery is not reasonable in light of the unchallenged new evidence and contributes to our conclusion that the NCD is not valid.

Conclusion

For the reasons explained above, we conclude that the AP has shown that NCD 140.3 is not valid under the reasonableness standard.

_____/s/
Leslie A. Sussan

_____/s/
Constance B. Tobias

_____/s/
Sheila Ann Hegy
Presiding Board Member

Overview of the Scientific Literature in the New Evidence

We provide below brief summaries of key findings in some of the studies submitted and reviewed by the Board as new evidence. The key findings in the remaining studies reviewed by the Board (also as new evidence) do not differ in any way material to our decision.

Jan Eldh, et al., *Long Term Follow Up After Sex Reassignment Surgery*, 31 Scand. J. Plast. Reconstr. Surg. Hand Surg. 39-45 (1997), AP Ex. 9. This study was a “long-term follow up of 136 patients operated on for sex reassignment ... to evaluate the surgical outcome” that divided MF and FM patients into “two groups according to the surgical technique: those operated on before 1986 and those operated on from 1986–1995.” The study found that after 1985 “the outcome of surgery became much better not only because of changes in management but also because of improvements in surgical technique, preoperative planning, and postoperative treatment,” that “[m]odern surgical techniques can give good aesthetic and functional results” and that “[p]ersonal and social instability before operation correlated with an unsatisfactory outcome of sex reassignment.” *Id.* at 39, 44, 45.

Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges*, 18 Ann. Rev. Sex Res. 178-224 (2007), AP Ex. 10. This study examined results of 18 international studies published between 1990 and 2006 that reported follow-up data of at least one year from 807 persons who had undergone sex reassignment surgery (193 FM, 614 MF). The purpose of this study was to update and assess the current validity of a conclusion in a 1990 article (based itself on review of 11 studies following post-operation) that transsexual surgery is an effective treatment for the alleviation of gender disorder in adults. This study concluded that “[d]espite methodological shortcomings of many of the studies . . . SRS is an effective treatment for transsexualism and the only treatment that has been evaluated empirically with large clinical case series” and that the “conclusion that SR [sex reassignment] is the most appropriate treatment to alleviate the suffering of extremely gender dysphoric individuals still stands: 96% of the persons who underwent SRS were satisfied and regret was rare.” The authors noted that the methodologies and designs of later studies were improved but that true randomized control studies are not feasible, and might be unethical for SRS. *Id.* at 178, 185, 215-16.

Ciro Imbimbo, M.D. Ph.D., et al., *A Report from a Single Institute’s 14-Year Experience in Treatment of Male-to-Female Transsexuals*, 6 J. Sex. Med. 2736-45 (2009), AP Ex. 13. This study’s aim was “to arrive at a clinical and psychosocial profile of male-to-female transsexuals in Italy through analysis of their personal and clinical experience and evaluation of their postsurgical satisfaction levels SRS.” From January 1992 to September 2006, 163 MF patients who had undergone SRS were asked to complete

patient satisfaction questionnaires. The study concluded that the “relatively high satisfaction level” was the result of a combination of “competent surgical skills, a well-conducted preoperative preparation program, and adequate postoperative counseling” Although postoperative pain and required revision surgeries were reported, the study found that 94% were satisfied with their post-surgical status and did not report regret. *Id.* at 2736, 2740, 2743.

Ladislav Jarolim, et al., *Gender Reassignment Surgery in Male-to-Female Transsexualism: A Retrospective 3-Month Follow-up Study with Anatomical Remarks*, 6 J. Sex. Med. 1635-44 (2009), AP Ex. 14. This study aimed “[t]o evaluate the results of surgical reassignment of genitalia in male-to-female transsexuals” by measuring “[s]exual functions and complications 3 months after surgery.” The study followed 134 patients who had undergone surgical procedures between 1992 and 2008 and described the evolution in surgical techniques since the 1950s. Although the study noted potential complications and risks specific to SRS (“such as impairment of urinary continence, fecal continence, intestinal fistula, urinary fistula, and necrosis of the skin graft”), it concluded that “[s]urgical conversion of the genitalia is a safe and important phase of the treatment of male-to-female transsexuals.” It also concluded that “[a]n increasing number of patients undergo this treatment because of the extensive progress in surgery involving the genitals and urethra” and that “[f]or male transsexuals, surgery can provide a cosmetically acceptable imitation of female genitals that enables coitus with orgasm.” *Id.* at 1635-36, 1642-43.

Annika Johansson, et al., *A Five-Year Follow-Up Study of Swedish Adults with Gender Identity Disorder*, 39 Arch. Sex. Behav. 1429-37 (2010), AP Ex. 15. This study evaluated from the perspective of both clinicians and patients the outcome of sex reassignment of “42 [MF and FM] transsexuals [who] completed a follow-up assessment after 5 or more years in the process or 2 or more years after completed sex reassignment surgery.” It found that “the outcome was very encouraging from both perspectives . . . with almost 90% enjoying a stable or improved life situation at follow-up and only six out of 42 (according to the clinician) with a less favorable outcome.” *Id.* at 1429, 1436.

G. Kockott, M.D. & E. M. Fahrner, Ph.D., *Transsexuals Who Have Not Undergone Surgery: A Follow-Up Study*, 16 Archives of Sexual Behavior 511-22 (1987), AP Ex. 17. This single-clinic study compared 26 transsexuals who sought but did not undergo surgery with 32 who did; psychosocial adjustment of those who delayed surgery did not improve from the time of diagnosis to follow-up while statistically significant positive changes in gender role, sexual, and socioeconomic adjustment were seen in transsexuals who had had surgery. *Id.* at 511, 517-19, 521.

Anne A. Lawrence, *Patient-Reported Complications and Functional Outcomes of Male-to-Female Sex Reassignment Surgery*, 35 Arch. Sex. Behav. 717-27 (2006), AP Ex. 21. This study “examined preoperative preparations, complications, and physical and

functional outcomes of [MF SRS] based on reports by 232 patients, all of whom underwent penile-inversion vaginoplasty and sensate clitoroplasty, performed by one surgeon using a consistent technique,” who were surveyed a mean of three years after surgery. The study found that “[r]eports of significant surgical complications were uncommon,” although one third had urinary stream problems, and that “[o]n average, participants expressed high levels of satisfaction with nearly all of the specific physical and functional outcomes of SRS.” *Id.* at 717, 719, 724.

Maria Inês Lobato, et al., *Follow-Up of Sex Reassignment Surgery in Transsexuals: A Brazilian Cohort*, 35 Arch. Sex. Behav. 711-15 (2006), AP Ex. 22. This small study examined the “impact of sex reassignment surgery on satisfaction with sexual experience, partnerships, and relationship with family members in ... 19 patients who received sex reassignment between 2000 and 2004.” The results “indicate[d] that SRS had a positive effect on different dimensions of the patients’ lives in all three aspects analyzed: sexual relationships, partnerships, and family relationships.” *Id.* at 711-12, 714.

Charles Mate-Kole, et al., *A Controlled Study of Psychological and Social Change after Surgical Gender Reassignment in Selected Male Transsexuals*, 157 Brit. J. Psychiatry 261-64 (1990), AP Ex. 23. This study reviewed 40 patients accepted for gender reassignment surgery, randomly assigned to have surgery early or later such that only half had had surgery by the time of a follow-up two years later. The study found that “[a]lthough the groups were similar initially, significant differences between them emerged at follow-up” Patients who received surgery were “seen to improve significantly as far as neurotic symptoms are concerned and to become more socially active” in comparison with the patients who had not yet received surgery. *Id.* at 261, 264.

Friedemann Pfafflin & Astrid Junge, *Sex Reassignment: Thirty Years of International Follow-Up Studies After Sex Reassignment Surgery: A Comprehensive Review 1961-1991* (Roberta B. Jacobson & Alf B. Meier trans., 1998) (1992), AP Ex. 25. This overview was completed in 1992 and published in English in 1998. It reviewed “30 years of international follow-up studies of approximately two thousand persons who had undergone sex reassignment surgery,” including “more than 70 individual studies and eight published reviews from four continents.” In general, more frequent and severe complications were found in the earlier years covered than in later reports. The overview concluded that “[s]ex reassignment, properly indicated and performed, has proven to be a valuable tool in the treatment of individuals with transgenderism,” that “gender reassigning treatments are effective” and that “the treatment that includes the whole process of gender reassignment is effective.” *Id.* at unnumbered pages 1, 45, 66-67.

Yolanda L.S. Smith, et al., *Sex Reassignment: Outcomes and Predictors of Treatment for Adolescent and Adult Transsexuals*, 35 Psychol. Med. 89-99 (2005), AP Ex. 27. This study evaluated “outcomes of sex reassignment, potential differences between subgroups

of transsexuals, and predictors of treatment course and outcome” in 162 adults (104 MF, 58 FM). The study found that “[a]fter treatment the group was no longer gender dysphoric,” had “improved in important areas of function, that 1-4 years after surgery, SR appeared therapeutic and beneficial . . . [and that] the vast majority expressed no regrets about their SR.” The study further concluded “that sex reassignment is effective” but that “clinicians need to be alert for non-homosexual male-to-females with unfavourable psychological functioning and physical appearance and inconsistent gender dysphoria reports, as these are risk factors for dropping out and poor post-operative results.” *Id.* at 89, 91, 96.

Svetlana Vujovic, M.D., Ph.D., et al., *Transsexualism in Serbia: A Twenty-Year Follow-Up Study*, 6 J. Sex. Med. 1018-23 (2009), AP Ex. 29. This study [a]imed to “describe a transsexual population seeking sex reassignment treatment in Serbia” by analyzing “data collated over a period of 20 years” from 147 transsexuals “applying for sex reassignment” of whom SRS was performed in 83% of MF and in 77% of MF patients. The study concluded that “in our population, there were no cases who regretted sex reassignment treatment,” which was attributed to diagnostic procedures used and the “young [adult] age at which our subjects embarked on treatment.” *Id.* at 1018-20, 1022.

Steven Weyers, M.D., et al., *Long-term Assessment of the Physical, Mental, and Sexual Health Among Transsexual Women*, J. Sex. Med. 752-60 (2009), AP Ex. 30. This study [a]imed “[t]o gather information on physical, mental, and sexual well-being, health-promoting behavior and satisfaction with gender-related body features of [49] transsexual women [MF] who had undergone SRS” with mean interval since vaginoplasty of 75.46 months. The study found that “sample . . . functions well after surgery on a physical, emotional, psychological and social level” and that “[o]nly with respect to sexuality do transsexual women appear to suffer from specific difficulties, especially concerning arousal, lubrication and pain.” *Id.* at 752, 754, 759.